ANNALS OF INTERNAL MEDICINE

Published Monthly by The American College of Physicians

VOL. 40, NO. 6 JUNE, 1954

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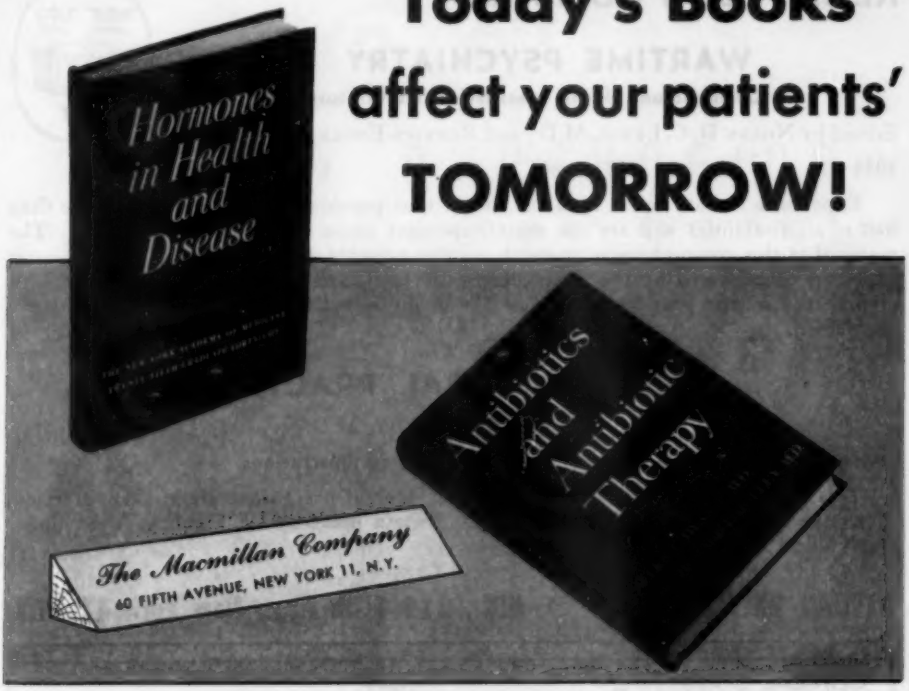
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2. Humphreys, P., *et al.*: Angiology *3*:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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1. McHardy and Browne: Sou. M.J. 45:1139, 1952.

2. Lorber and Shay: Fed. Proc. 12:90, 1953.

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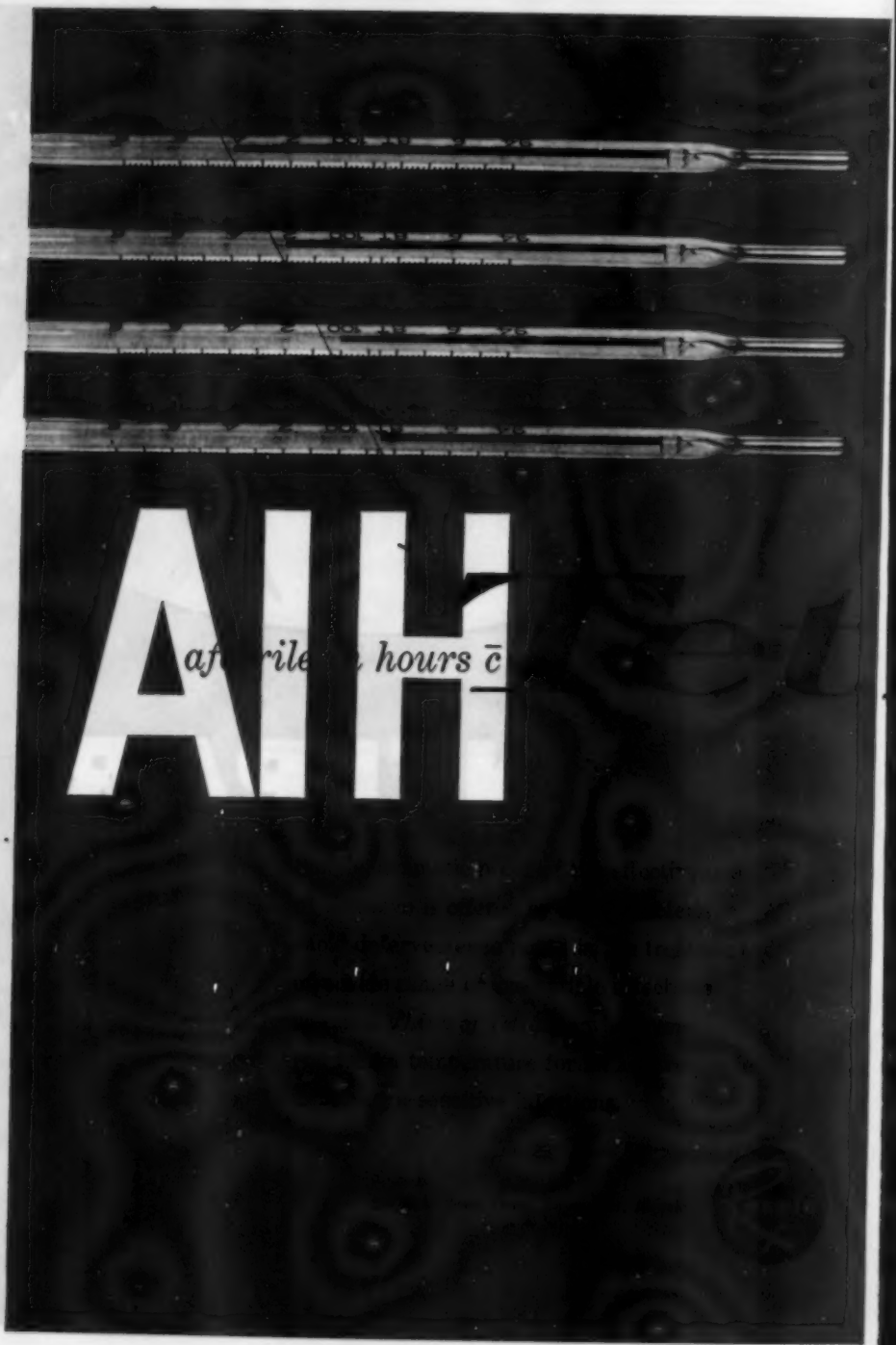
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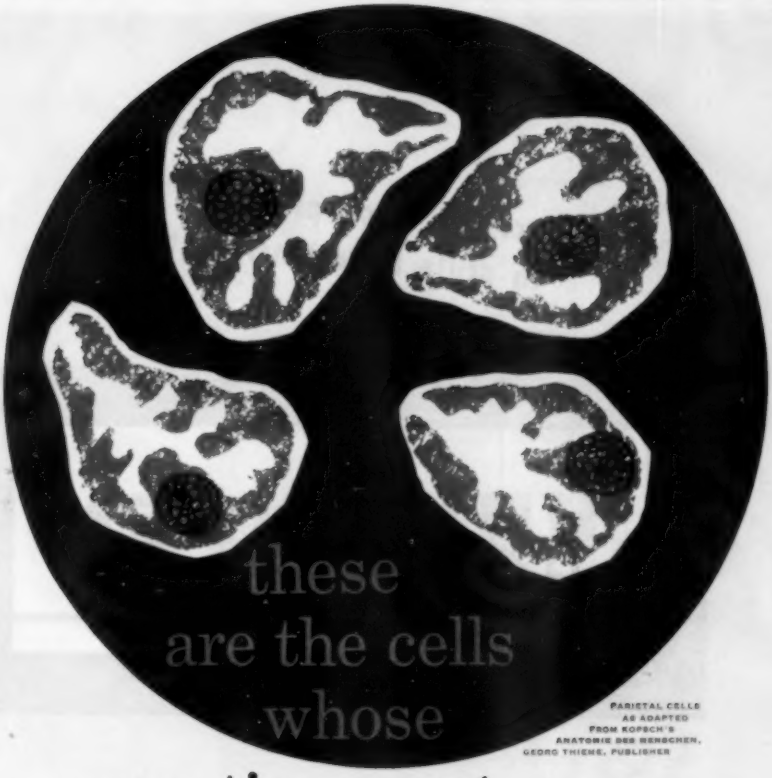
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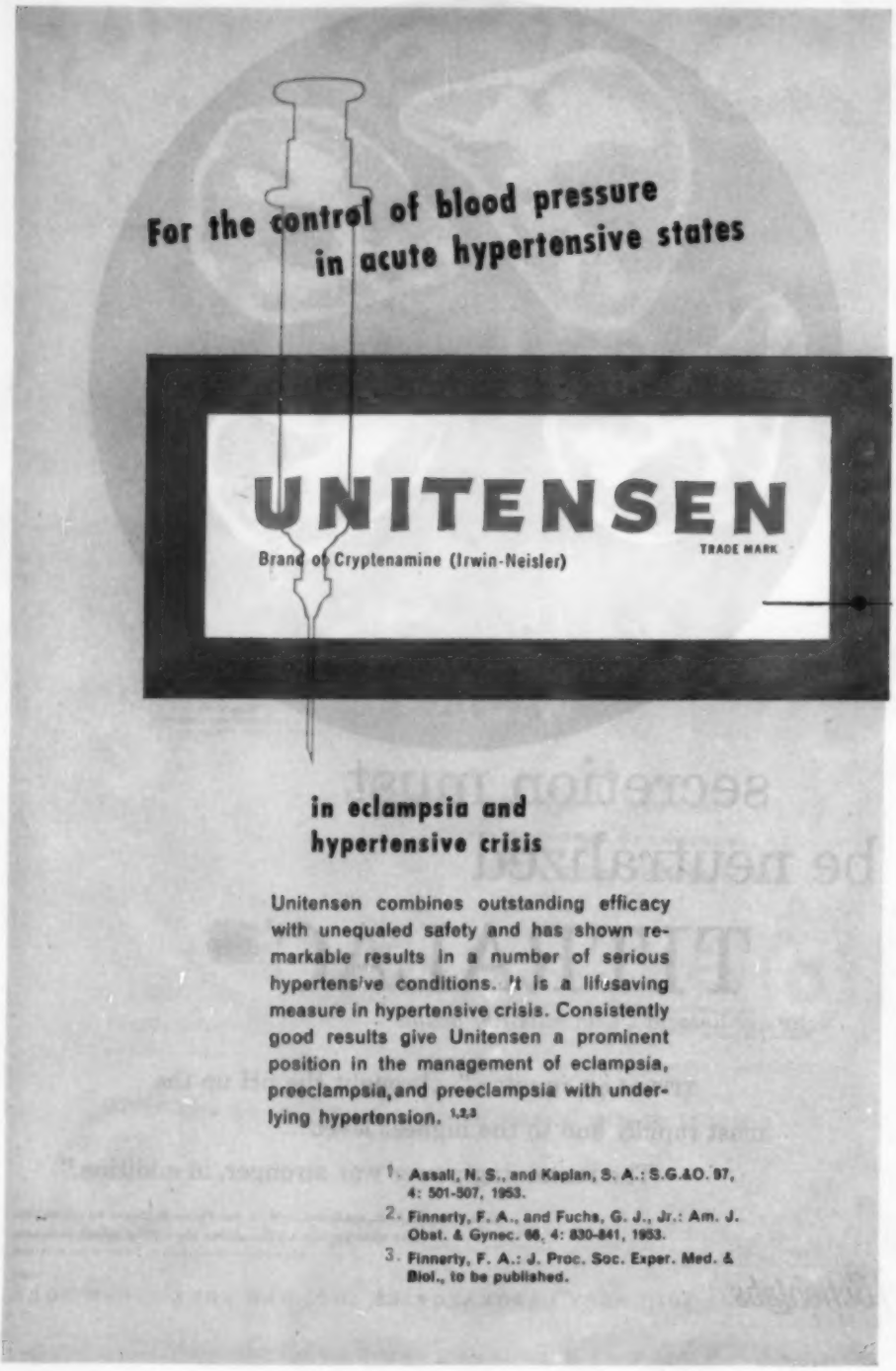
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1. Assali, N. S., and Kaplan, S. A.: S.G.&O. 97, 4: 501-507, 1953.
2. Finnerty, F. A., and Fuchs, G. J., Jr.: Am. J. Obst. & Gynec. 66, 4: 830-841, 1953.
3. Finnerty, F. A.: J. Proc. Soc. Exper. Med. & Biol., to be published.

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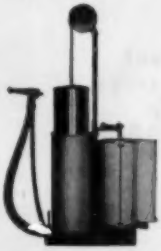
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without side effects

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- all "essential" vitamins and minerals including vitamins A, B_{12} and E; calcium, phosphorus, iron, cobalt, and other trace minerals.
- moderate in cost

Available in bottles of 30, 50, 100 and 500 capsules.

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just one capsule provides:

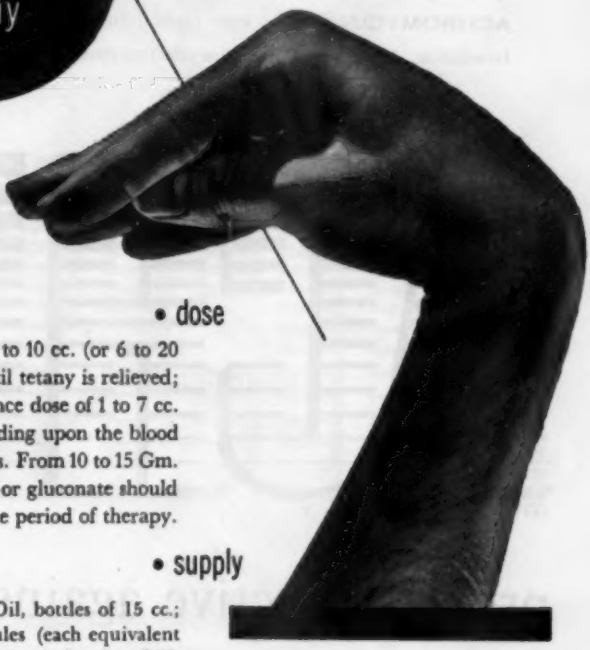
Vitamin A*	25,000 U.S.P. Units
Vitamin D*(calciferol)	1,000 U.S.P. Units
Ascorbic Acid (C)	150 mg.
Thiamine HCl (B_1)	10 mg.
Niacinamide	100 mg.
Riboflavin (B_2)	5 mg.
Pyridoxine HCl (B_6)	1 mg.
Vitamin B_{12}	5 mcg.
d, Calcium Pantothenate	5 mg.
dl, Alpha Tocopheryl Acetate (E)*	5 mg.
Dicalcium Phosphate (Calcium 58 mg.) (Phosphorus 45 mg.)	200 mg.
Ferrous Sulphate Exsiccated (Iron 30 mg.)	100 mg.
Copper	1.5 mg.
Iodine	0.1 mg.
Manganese	1 mg.
Magnesium	6 mg.
Zinc	1 mg.
Cobalt	0.1 mg.
Molybdenum	0.2 mg.

*Oil-soluble vitamins made water-soluble with sorethytan esters; protected by U. S. Patent 2,417,299.

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Orally 3 to 10 cc. (or 6 to 20 capsules) daily until tetany is relieved; weekly maintenance dose of 1 to 7 cc. or 2 to 14 capsules depending upon the blood and urine calcium levels. From 10 to 15 Gm. calcium lactate or gluconate should be given daily through the period of therapy.

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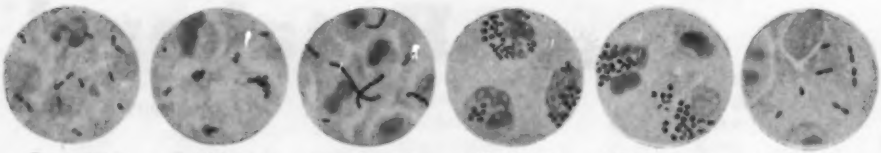
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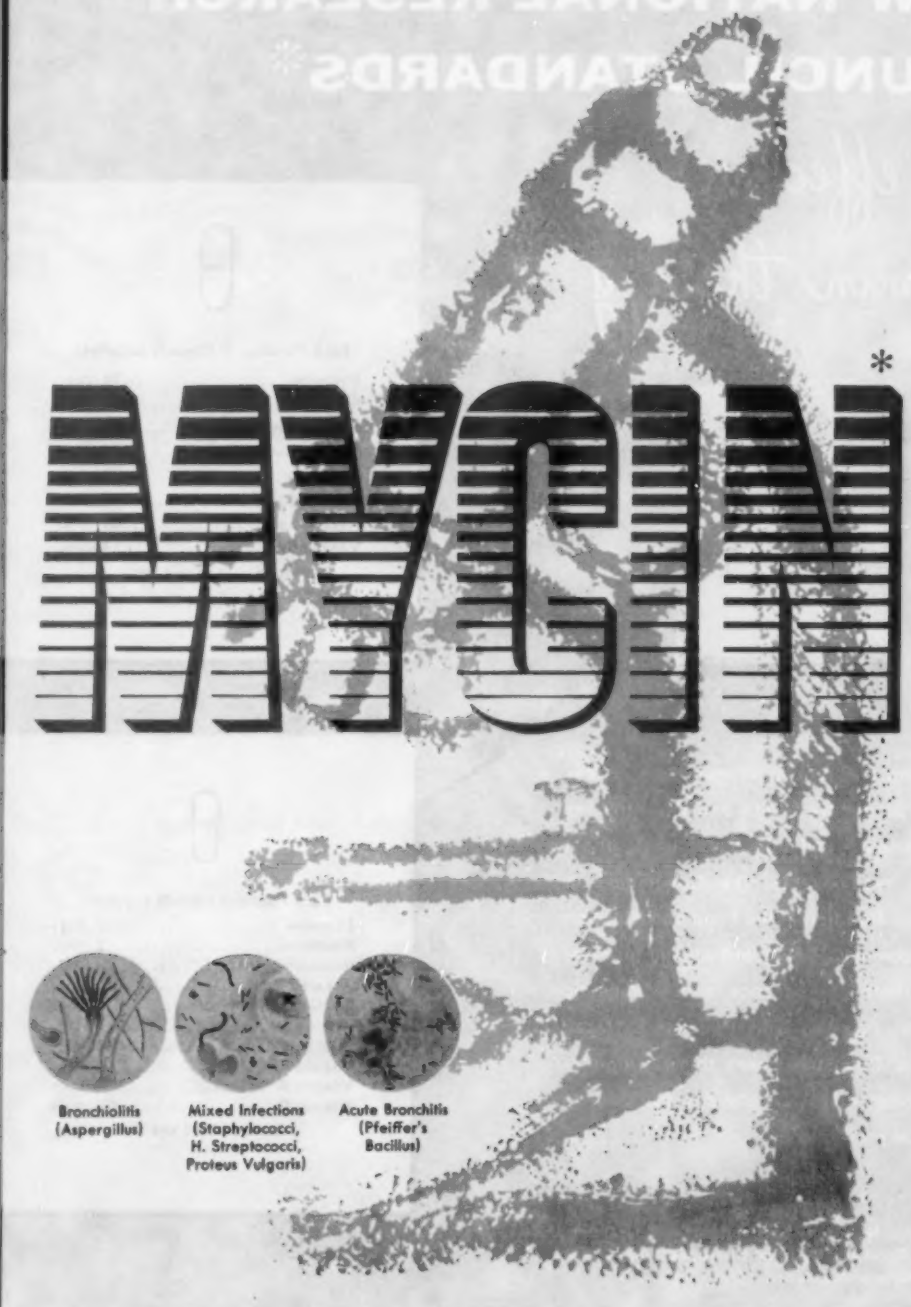
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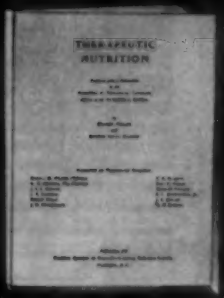
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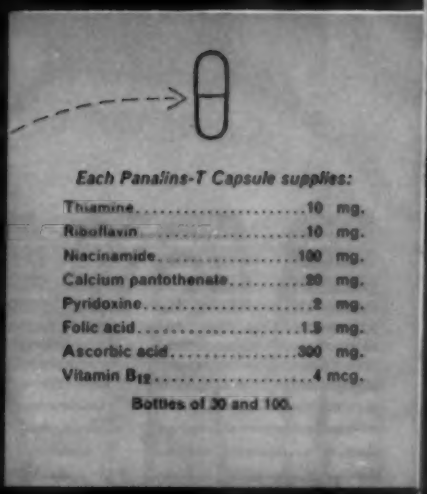

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Bronchiolitis (Aspergillus)
Mixed Infections (Staphylococci, H. Streptococci, Proteus Vulgaris)
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NEW NATIONAL RESEARCH COUNCIL STANDARDS*

for effective vitamin therapy



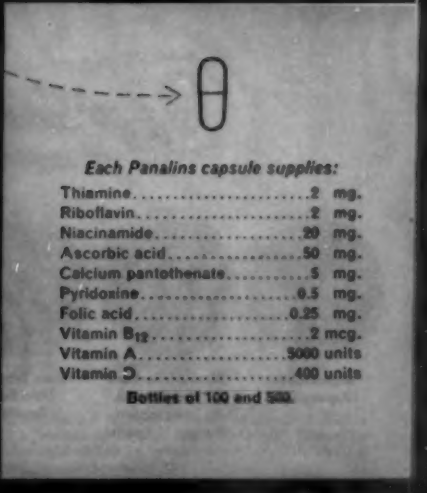
Emphasizing that regular vitamin intake is essential to productive health and that stresses such as disease and injury profoundly affect nutritional requirements, the Committee on Therapeutic Nutrition of the Food and Nutrition Board* recommends standard vitamin formulations for both maintenance and therapeutic dosage. In Panalins and Panalins-T, Mead Johnson & Company makes these authoritatively recommended formulations available to the medical profession.



Each Panalins-T Capsule supplies:

Thiamine	10 mg.
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Niacinamide	100 mg.
Calcium pantothenate	20 mg.
Pyridoxine	2 mg.
Folic acid	1.5 mg.
Ascorbic acid	300 mg.
Vitamin B_{12}	4 mcg.

Bottles of 30 and 100.



Each Panalins capsule supplies:

Thiamine	2 mg.
Riboflavin	2 mg.
Niacinamide	20 mg.
Ascorbic acid	50 mg.
Calcium pantothenate	5 mg.
Pyridoxine	0.5 mg.
Folic acid	0.25 mg.
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Vitamin A	5000 units
Vitamin D	400 units

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* Therapeutic Nutrition, Committee on Therapeutic Nutrition, Food and Nutrition Board, Publication 234, National Research Council.

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Panalins-T supplies important water-soluble vitamins in the high therapeutic potencies needed to promote optimal recovery from disease or injury. Since the body cannot store appreciable amounts of these vitamins, regular provision of generous amounts is essential.

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- patients undergoing mild physiologic and pathologic stresses

*Therapeutic Nutrition, Publication No. 234, National Research Council.

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Lester M. Morrison, M.D., Los Angeles, in Rev. Gastroenterology, 20:744 (Oct.) 1953; abstract in J.A.M.A. 153:1580 (Dec. 26) 1953.

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large gastric ulcer



Fig. 3, Case 103 before therapy.

healed with



Fig. 6, Case 103 after 4 months PRANTAL therapy.
* Heineken, T. S.: Rev. Gastroenterol. 20:829, 1953.

PRANTAL...*relieves pain*

*facilitates healing • "least side actions"**

widest variety of dosage forms

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estrogen-progesterone effective in menstrual disturbances:

Each scored tablet contains:

Estrogenic Substances* .. 1 mg. (10,000 I.U.)

Progesterone .....30 mg.

**Naturally-occurring equine estrogens (consisting primarily of estrone, with small amounts of equilin and equilenin, and possible traces of estradiol) physiologically equivalent to 1 mg. of estrone.*

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1. *Rossett, N. E., and others: Ann. Int. Med.* 36:98 (*Jan.*) *1952*

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d-Amphetamine Phosphate (dibasic)	5 mg.
Nicel*	150 mg.

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Controlled Study of

Metamine.

Triethanolamine trinitrate biphosphate, Leeming, tablets, 2 mg.

Clinical excellence

SUMMARY[1] (*From the Department of Medicine, McGill University*)

Condition of Patients	Daily number of anginal attacks during: Control period (3-4 weeks)	Placebo A (3 weeks)	METAMINE (3 weeks)	Placebo B (3 weeks)
1. Angina of effort, coronary occlusion; man, 53 years old	Average: 7 Range: 5-12	Average: 8 Range: 5-11	Average: 0.75 Range: 0-8	Average: 5.5 Range: 1-9
2. Angina of effort; man, 45 years old	Average: 9 Range: 7-12	Average: 7 Range: 5-12	Average: 4 Range: 0-6	Average: 4.4 Range: 3-6
3. Angina of effort; man, 50 years old	Average: 4.5 Range: 3-6	Average: 4.2 Range: 2-8	Average: 2.6 Range: 0-3	Average: 4.5 Range: 3-8
4. Angina of effort, coronary occlusion; man, 40 years old	Average: 6.5 Range: 4-9	Not administered	Average: 3.5 Range: 0-5	Average: 6.5 Range: 4-9
5. Angina of effort, coronary occlusion; man, 57 years old	Average: 7.2 Range: 2-10	Average: 8 Range: 3-12	Average: 3.5 Range: 0-8 (8 days only)	Not administered because patient developed upper respiratory infection.

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Numerous clinical and experimental studies since 1946 indicate that METAMINE is ideally suited for routine prevention of anginal attacks because of low (2 mg.) effective dose, prolonged action, and exceptional freedom from side effects. Taken routinely, METAMINE prevents attacks of angina pectoris or greatly diminishes their number and severity.[1] The entire circulation appears to benefit,[2] and the anginal patient may resume a life of useful activity under continuing treatment with this new, low-dose, long-acting coronary vasodilator.

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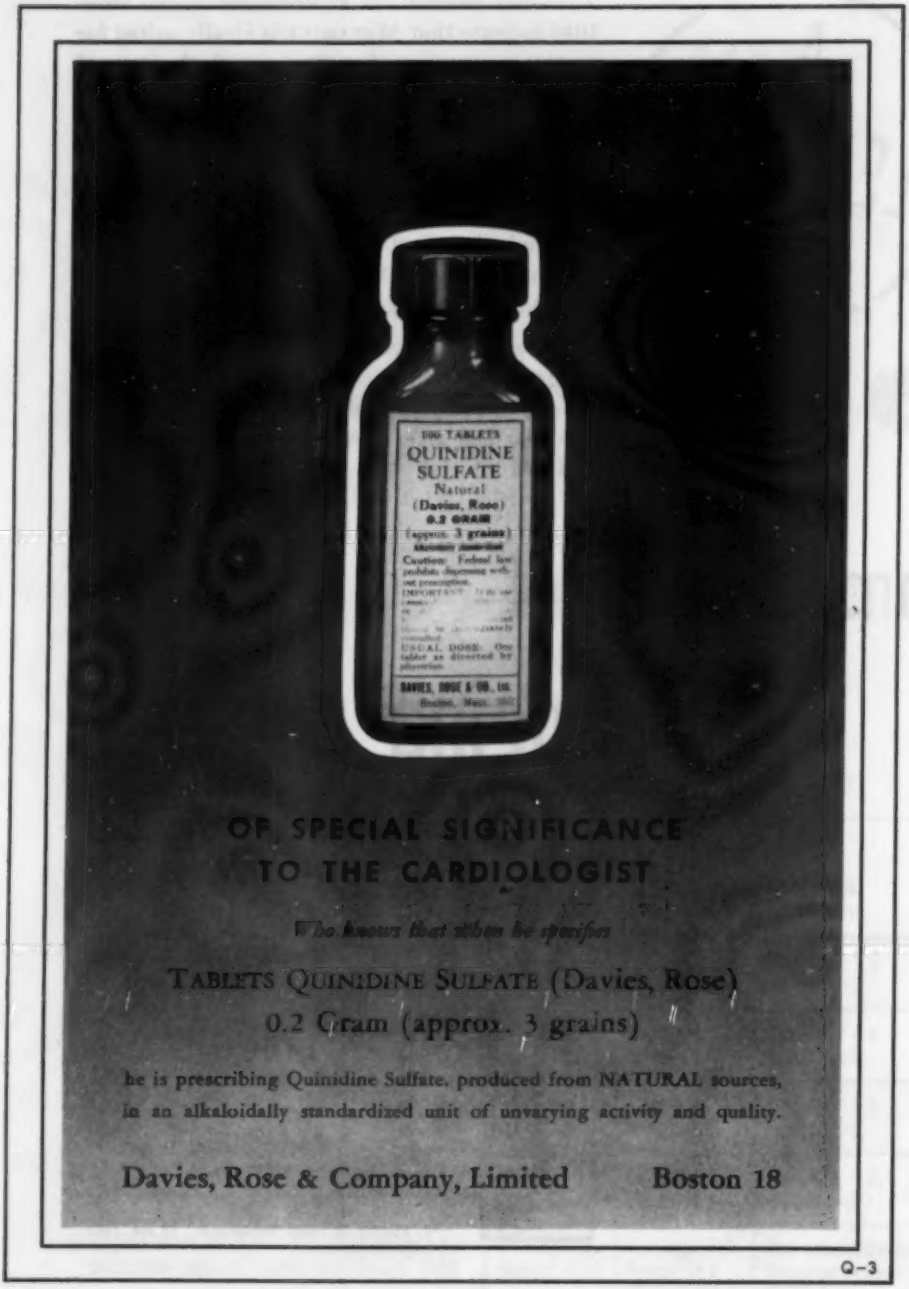
angina pectoris



References:

1. Palmer, J.H., and Ramsey, C.G.: Canadian M.A.J., 65:16, July, 1951.
2. Pfeiffer, H.: Klin. Wochenschr., 28:304, 1950.

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Who knows that when he specifies
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he is prescribing Quinidine Sulfate, produced from NATURAL sources,
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dramatic relief even in the "refractory" patient

Even asthmatics who have proved refractory to all customary measures including epinephrine (and even to other forms of ACTH) may benefit dramatically from HP*ACTHAR *Gel*.

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When used early enough, HP*ACTHAR *Gel* may become a valuable agent in prolonging the life span of the asthmatic. The authoritative Journal of Allergy stresses: ACTH "should not be withheld until the situation is hopeless." [1]

1. Editorial, J. Allergy 23: 279, 1952.

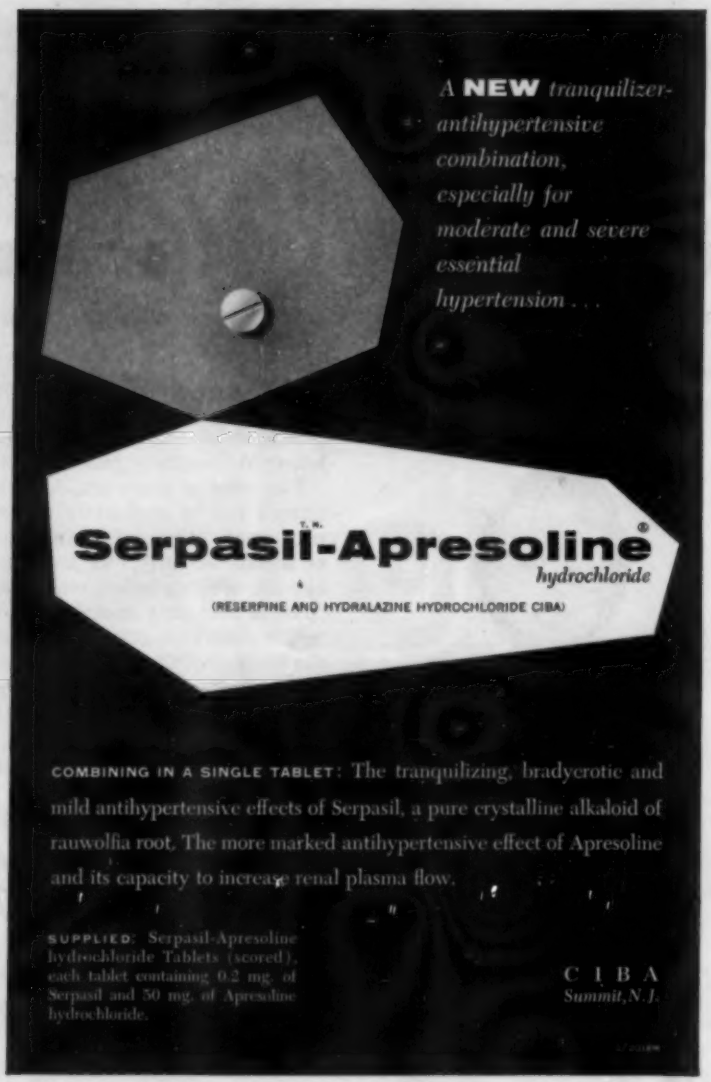
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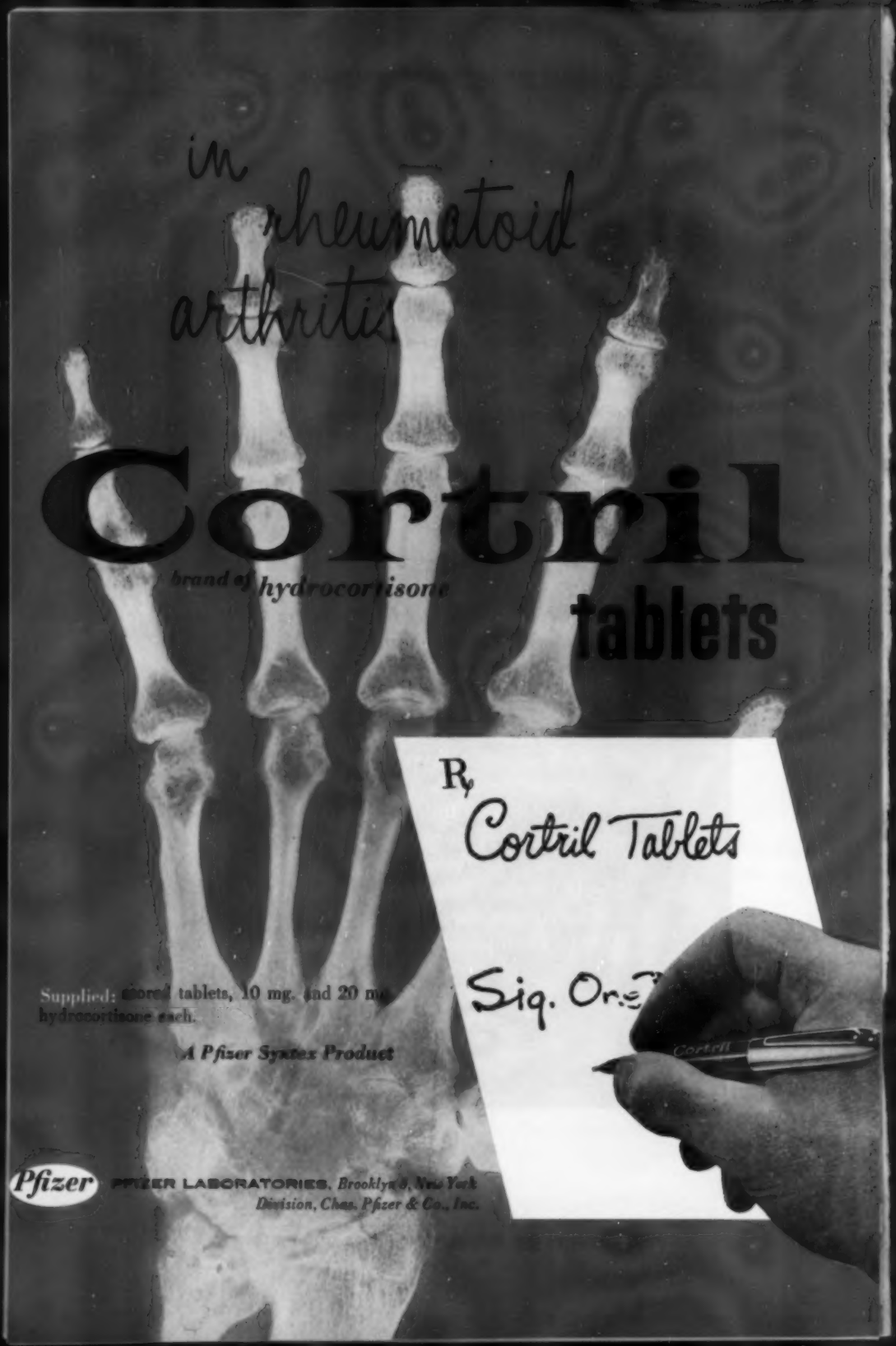
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Many anemic patients continue to show a subnormal blood picture despite adequate iron therapy. Furthermore, ample systemic iron reserves have been demonstrated in many markedly anemic patients. In such cases, depression of the hemopoietic function due to bacterial or virus infection, or to allergy, is very frequently the cause of the anemia.

This accounts for the poor response so often reported where iron alone has been given[1], in "low-grade anemias" of children[2], nutritional anemia[3] and other forms of "secondary" anemia.

Such limited response has raised the question—is iron the complete answer to basic anemia therapy?

Recent research[4,5] suggests that the answer is NO—a more *basic* approach should aim at stimulating the depressed bone marrow, the "organ" responsible for effecting erythrogenesis, mobilization of iron reserves and hemoglobin synthesis.

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The First True Hemopoietic Stimulant

Roncovite offers, for the first time, the specific bone marrow hemopoietic action of well-tolerated cobalt plus adequate supplementary iron for those lacking in "systemic iron reserves."

In iron deficiency anemia—

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The patient often voluntarily reports an increased sense of well-being *within a few days*—as reported by documented clinical evidence.

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Age in Mos.	Complicating Illness	R. B. C. Increase per day	Hgb. Increase per day
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3	None	113,000	0.22 Gm.
17	None	74,000	0.15 Gm.
5	Acute Laryngo-Tracheitis	—500	—0.01 Gm.
10	None	79,000	0.22 Gm.
15	None	133,000	0.20 Gm.
3½	Infantile Diarrhea	19,000	0.03 Gm.
11	None	26,000	0.07 Gm.
17	Herpetic Stomatitis	100,000	0.11 Gm.
9	None	159,000	0.11 Gm.
14	None	155,000	0.14 Gm.
12	Cervical Lymphadenopathy	165,000	0.12 Gm.
15	None	68,000	0.10 Gm.
13	None	190,000	0.28 Gm.
6	Gastro-enteritis	198,000	0.16 Gm.
9	None	42,000	0.09 Gm.
24	None	81,000	0.16 Gm.
19	Fever	78,000	0.15 Gm.
7	Urinary Infection	134,000	0.10 Gm.
24	None	122,000	0.15 Gm.
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12	None	107,000	0.15 Gm.
15	None	134,000	0.10 Gm.

SUPPLIED:

Roncovite Tablets—enteric coated, red. Each contains cobalt chloride, 15 mg.; ex. ferrous sulfate, 0.2 Gm.; bottles of 100.
Dose: one tablet 4 times a day.

Roncovite Drops—each 0.6 cc. contains cobalt chloride, 40 mg.; ferrous sulfate, 75 mg.; bottles of 15 cc. with calibrated dropper.
Dose: 0.6 cc. daily.

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Continued on page 80

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*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, Philadelphia, The Blakiston Company, 1950, p. 655.

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*"Therapeutic Nutrition, Publication No. 334, National Research Council.

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1. Zelman, S.: Arch. Int. Med. 90:141, 1952.

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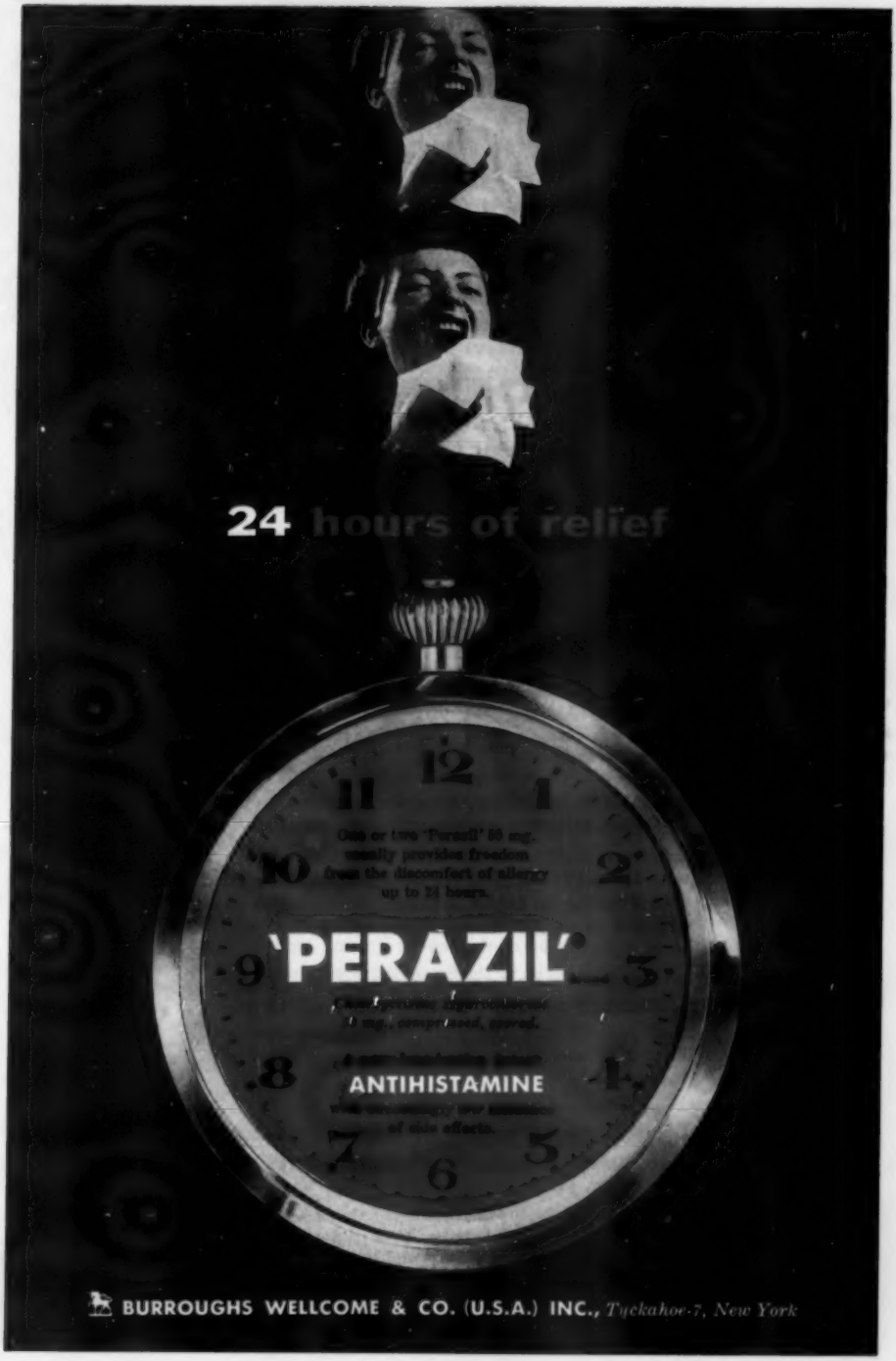
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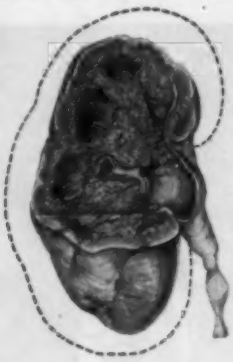
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*Talkov, R. H., Ropes, M. W., and Bauer, W.: *The Value of Enteric Coated Aspirin.* N.E.J. Med. 242,19 (Jan. 5) 1950.

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PHOTOGRAPH BY PAUL RADKAI

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REFERENCE: 1. J. Pediat. 42:292 (March) 1953.

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ANNALS OF
INTERNAL MEDICINE

VOLUME 40 JUNE, 1954 NUMBER 6

VALUE OF MECHANICAL AIDS IN THE MANAGEMENT OF A PATIENT WITH POLIOMYELITIS *

By GUSTAV J. BECK and ALVAN L. BARACH, F.A.C.P., *New York, N. Y.*

THE purpose of this paper is to describe the value of mechanical methods of aiding the functions of the respiratory system in patients with bulbar poliomyelitis in whom inability to expectorate produces severe and chronic breathing difficulties. The chief measures employed included exsufflation with negative pressure and an abdominal belt of the type used in the treatment of pulmonary emphysema [1-6]; a case report illustrates the therapeutic response to these measures and, in addition, the mental and physiologic effects of artificial respiration without changes in lung volume.

METHODS

A Description of the Physiologic Principles Involved in the Clinical Application of Exsufflation with Negative Pressure, the Rocking Bed and the Immobilizing Lung Chamber: Exsufflation with Negative Pressure (E.W.N.P.) is a physical method of producing physiologic effects which simulate those of an effective cough. A nearly maximal inflation of the lung is followed by a mechanically produced expiratory cycle in which air leaves the lungs at a velocity similar to that of the vigorous cough of a normal subject. Inspiration is produced by a motor blower unit over a period of 1 to 2 seconds, with a peak positive mask pressure of 20 to 40 mm. Hg; the sudden opening of a solenoid valve connects the mask on the face to the vacuum side of the blower, which operates under a negative pressure of 40 mm. Hg below the atmosphere. A pressure drop of 60 to 80 mm. Hg achieved in this manner is accompanied by a high expiratory flow rate from

* Presented at the Thirty-fifth Annual Session, American College of Physicians, Chicago, Illinois, April 7, 1954.
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This study was aided by a grant of the National Foundation for Infantile Paralysis.

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the respiratory tract, as a result of which mucopurulent plugs may be brought to the trachea and expectorated.

The rocking bed is a ventilating device which produces inflation and deflation of the lungs by tilting the patient footward or headward, respectively. During the inspiratory phase the diaphragm is lowered. The intra-abdominal content forces the diaphragm upward to produce the expiratory cycle.

The lung immobilizing chamber (equalizing pressure chamber) employs changes in air density to produce pulmonary ventilation without the need for voluntary breathing or movement of the chest wall. The pressure surrounding the entire body is changed 25 times per minute, from 55 mm. Hg above the atmosphere to 55 mm. Hg below the atmosphere. This pressure change, about one seventh of an atmosphere, results in a movement of air in and out of the lungs amounting to one seventh of the air remaining in the lungs at the end of the expiratory phase. Assuming a functional residual air value of 2,800 c.c., the tidal air exchange produced by a pressure change of 110 mm. Hg would be 400 c.c. Since there is a delay of air movement from the mouth to the alveoli produced by the resistance of the tracheobronchial tree, a similar resistance of the wave of pressure surrounding the body is introduced between the head and body by means of a baffle around the neck region. A pressure differential of 4 to 6 cm. of water thus created between the head and thorax insures the simultaneous arrival of air inside and outside the thoracic wall during inspiration and expiration, with the result that adequate ventilation is provided in the absence of thoracodiaphragmatic motion.

Case Report

A 29 year old male became ill with spino-encephalitic poliomyelitis during November, 1952. Following a stormy course, complicated by mental disorientation and hypertension over a period of one month, severe respiratory insufficiency due to involvement of most of the thoracic and diaphragmatic musculature became evident. He stayed in a tank-type respirator nearly continuously for three months. A severe upper respiratory infection resulted in the accumulation of mucopurulent secretions in the tracheobronchial tree. Little relief of dyspnea and cyanosis was obtained by nearly continuous suction by a catheter through a tracheotomy tube and, in February, 1953, the severity of the symptoms of respiratory insufficiency increased markedly, fever to 102° F. occurred, and periods of irrational behavior complicated his course. Antibiotic therapy had provided no relief.

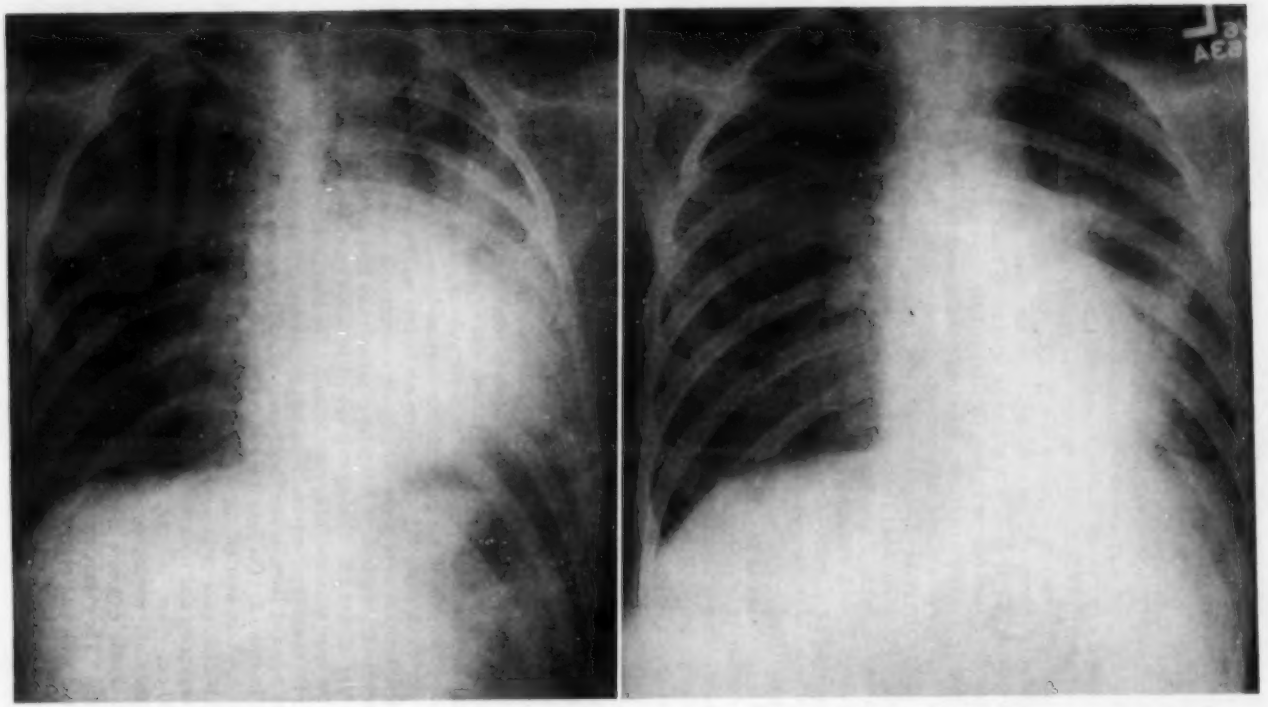
He was completely unable to cough up the thick tenacious secretions from his respiratory tract, and on February 11, 1953, when first seen by one of us, his vital capacity, without the assistance of the respirator, was 400 c.c. The use of "Exsufflation with Negative Pressure" (E.W.N.P.) with five to six exsufflations, repeated eight times at one minute intervals every half-hour, resulted in almost immediate elimination of 120 ml. of thick mucopurulent secretions through the tracheotomy tube and mouth. Fever, dyspnea and cyanosis were markedly diminished within 24 hours, and after 72 hours he was able to remain outside the respirator for two to three hours, two to three times a day.

On February 18 the vital capacity had risen to 500 c.c. and the tracheotomy tube was removed. The patient improved progressively and was comfortable for five hours on the rocking bed, and in the respirator during the remaining time. E.W.N.P. was employed every three to four hours each day. During the following two weeks he was removed from the respirator to a rocking bed for 14 hours of the day. Treatment with E.W.N.P. was continued to prevent re-accumulation of secretions. On March 13, 1953, he was compietely weaned from the respirator to the rocking bed. The vital capacity on March 16 was 535 c.c. before E.W.N.P., and 690 c.c. immediately after E.W.N.P. The sputum was slightly purulent, with *Bacillus pyocyaneus* on culture on two occasions. E.W.N.P. three to four times a day resulted in elimination of sputum and removed subjective sensations of respiratory embarrassment immediately. E.W.N.P. was gradually reduced to twice daily; by April 15 the rocking bed was needed only at night. On May 6, 1953, the vital capacity was 520 c.c.

On May 17 a severe respiratory infection was followed by dyspnea, malaise and fever. The patient was placed on a regimen of hourly E.W.N.P. and produced large amounts of grossly purulent sputum which, on culture, revealed the presence of *B. pyocyaneus*. Penicillin and Terramycin were administered without improvement. The chest was normal to percussion and ascultation on May 19, 1953. At the patient's request E.W.N.P. was discontinued for three hours during the night of May 19. On the morning of May 20, because of the severity of dyspnea and cyanosis, he was placed continuously on the rocking bed, and in the afternoon a sudden onset of severe left chest pain took place, with dullness to percussion and absent breath sounds at the left base. X-rays of the chest at 7:30 p.m. showed a marked shift of the heart towards the left, mild contraction of the left intercostal spaces, elevation of the left leaf of the diaphragm, and numerous mottled partially confluent densities occupying most of the left lung. The diagnosis of atelectasis of the left lower lobe was confirmed radiologically (figure 1).

The patient's schedule of treatment with E.W.N.P. was changed to every half hour. After 12 hours, signs of definite aeration of the left lower lobe were present on auscultation, with considerable improvement of the x-ray findings and with return of the diaphragm to its normal position and reduced mediastinal shift. Initially during each treatment with E.W.N.P. blood-streaked purulent plugs 1 to 3 cm. in length were coughed directly into the trap between the patient's mouth and the exsufflator valve. Within three hours the sputum became thinner and mucopurulent in consistency. Clinically, the patient's cyanosis and dyspnea were completely relieved overnight. Because of the persistence of fever and the presence of *B. pyocyaneus* in the sputum, polymyxin-B was given for six days in doses of from 100 to 200 mg. by aerosol. For three days, 100 mg. polymyxin-B, one million units of penicillin and 1 gm. of streptomycin were given daily by intramuscular injection. Gradual decrease in fever occurred. Because of fatigue the patient was kept in the respirator for 24 hours on May 22 and 23. During that period E.W.N.P. was required every hour to eliminate the large quantities of sputum formed. On May 24 the patient was markedly improved; the quantity of expectoration was diminished and the use of E.W.N.P. was reduced to two and later to four hour intervals. The events during his illness are illustrated in figure 2. On June 3 his vital capacity had risen to 800 c.c. Thereafter, the patient has been kept off the rocking bed for 16 to 18 hours a day, during which he uses E.W.N.P. once or twice daily as a "booster" whenever he feels the need for assisted respiration and for removal of secretions. His vital capacity on September 20 was 930 c.c.

Diaphragmatic motion during E.W.N.P. was observed fluoroscopically and recorded on double exposure x-rays in a normal individual and in the patient with poliomyelitis. The excursion in the normal subject during E.W.N.P. was 8 cm., and was identical with that observed during a cough of maximal effort. The diaphragm



A B

FIG. 1. X-rays of the patient's chest showed a left lower lobe atelectasis (A). Treatment with E.W.N.P. every one-half hour resulted in aeration of the left lower lobe of the lung within 12 hours (B).

of the patient with poliomyelitis was 0.5 cm. higher during the expiratory than the inspiratory phase during his natural cough. However, the diaphragmatic excursion during E.W.N.P. was marked, the leaves being 6.5 cm. higher during expiration than during inspiration. The effect of the pressure change of E.W.N.P. on the diaphragm, as seen in figures 3 and 4, is similar to that of an effective normal cough.

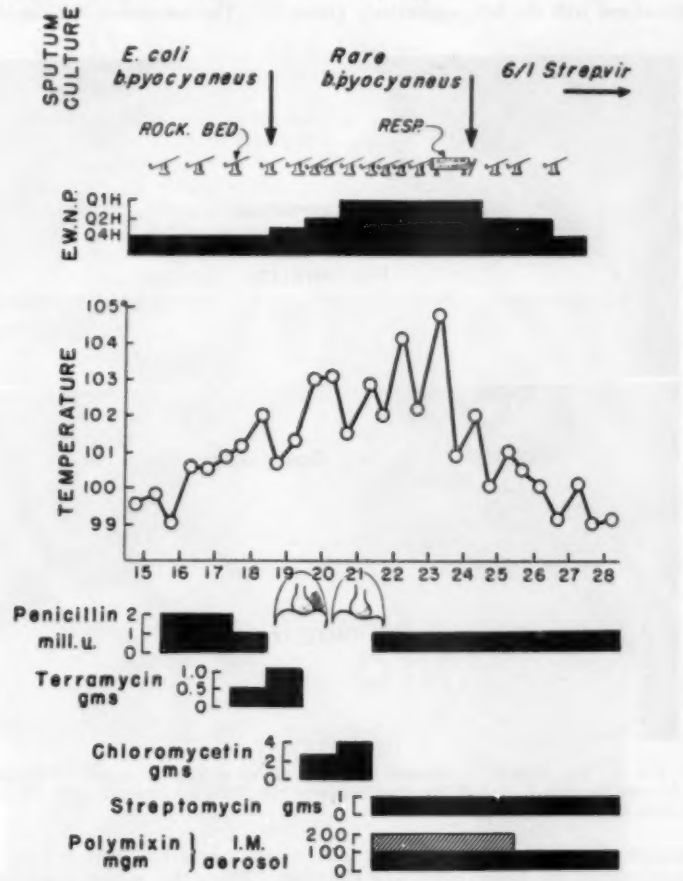


FIG. 2. During the course of a severe pulmonary infection produced by *B. pyocyaneus*, the complicating atelectasis was aerated in 12 hours by means of E.W.N.P. Polymyxin-B was administered in intramuscular and aerosol form, in conjunction with penicillin and streptomycin, resulting in subsidence of dyspnea and fever within 48 hours and elimination of *B. pyocyaneus* from the sputum.

An important contribution to the patient's ventilatory function was made when it was observed that the patient's effort in ventilation was markedly decreased following the application to the suprapubic area of an especially designed belt which

supported his viscera and raised the level of the diaphragm.* This improvement was reflected in an immediate reduction of the pulmonary ventilation from 8,077 to 6,865 c.c. per minute, the respiratory rate falling from 27 to 15 per minute, as seen in figure 5. The arterial oxygen saturation was 89.4 per cent before and 89.5 per cent after wearing the belt for one hour, respectively. During the same test, the partial pressure of serum CO_2 was 51 and 45 mm. Hg, and the pH was 7.31 and 7.33 without and with the belt, respectively (table 1). The maintenance of the blood gas

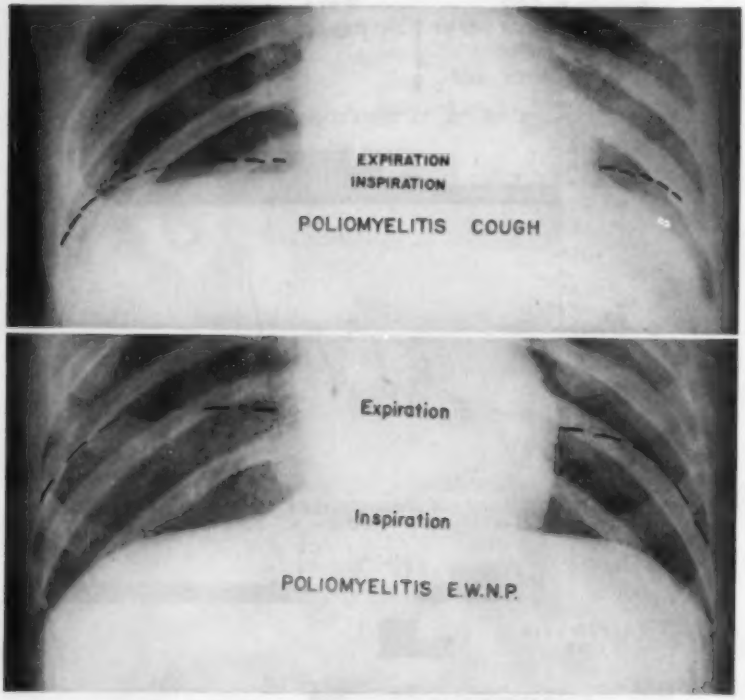


FIG. 3. The patient's spontaneous cough produces an expiratory rise of the diaphragm of 0.5 cm. During E.W.N.P. the diaphragmatic rise from the inspiratory to the expiratory position is 6.5 cm.

composition, despite the reduction in total minute ventilation, indicated that alveolar ventilation of the lower lobes was improved. When this patient was tilted head down at an angle of 20 degrees, a primarily thoracic accessory muscle type of respiration observed in the sitting position was changed to a predominantly diaphragmatic type, with a fall in ventilation from 8,500 to 7,600 c.c. per minute. During the inhalation of 100 per cent oxygen the minute volume of ventilation was further reduced to 5,900 c.c. The vital capacity in the sitting position was 600 c.c. as com-

* The G.B. emphysema belt and weighted abdominal jacket, which provide an upward and backward pressure on the lower abdomen, may be obtained from the Spencer Co., New Haven, Conn.

TABLE I

	Sitting without Belt	Sitting with Belt
Respiratory Rate	27	15
Pulmonary Ventilation	8,077	6,865
Arterial Oxygen Saturation	89.4	89.5
pCO_2	51	45
pH	7.31	7.33

pared to 400 c.c. head down, which indicated that increased diaphragmatic excursion produced a more efficient gas exchange even in the presence of a lowered vital capacity.

The ventilatory responses of this patient to the head-down position and inhalation of oxygen were similar to those produced in patients with pulmonary emphysema in whom a more efficient aeration of the lower lobes of the lungs was induced by the head-down position, the viscera in this instance elevating the diaphragm.[4, 5]

Diaphragmatic breathing, with prompt abandonment of upper intercostal respiration, was also induced by applying a jacket weighing 12 pounds to the lower abdomen. This reaction again suggested decreased lung elasticity or compliance, as

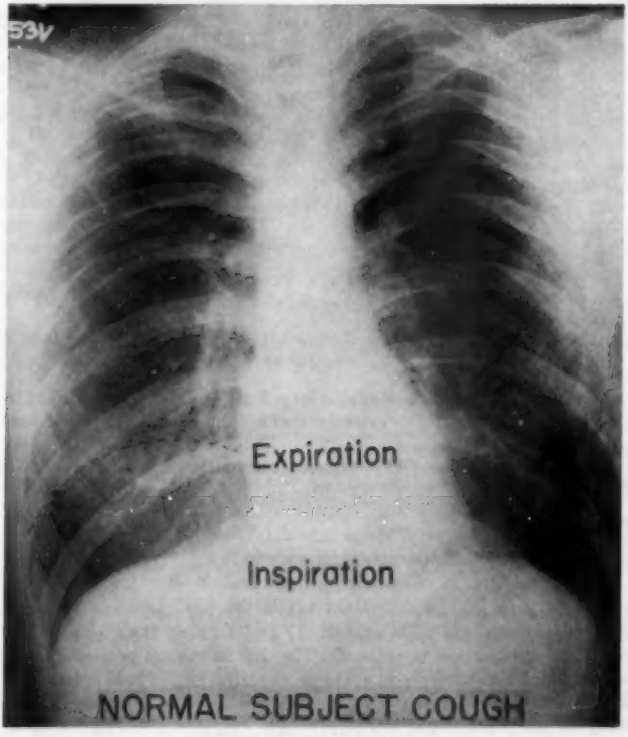


FIG. 4. During the natural cough of a normal subject there is an 8 cm. excursion of the diaphragm from the inspiratory to the expiratory position.

found by others.[7, 8] The value of elevating the diaphragm is the promotion of some degree of increased diaphragmatic movement and better aeration of the bases of the lungs in cases in which the diaphragmatic muscle has a potential ability to contract.

Additional evidence to support the concept above described was obtained by placing the patient in a tank respirator and applying continuous positive pressure to the body. With a positive intra-tank pressure of 6.0 cm. H_2O during inspiration and expiration the pulmonary ventilation was lowered from 7,250 to 5,500 c.c. per minute. When the chamber pressure was again returned to atmospheric pressure, the ventilation returned to 7,100 c.c. per minute. The character of respiration was noticeably changed by a lessened activity of the accessory chest and neck musculature. The

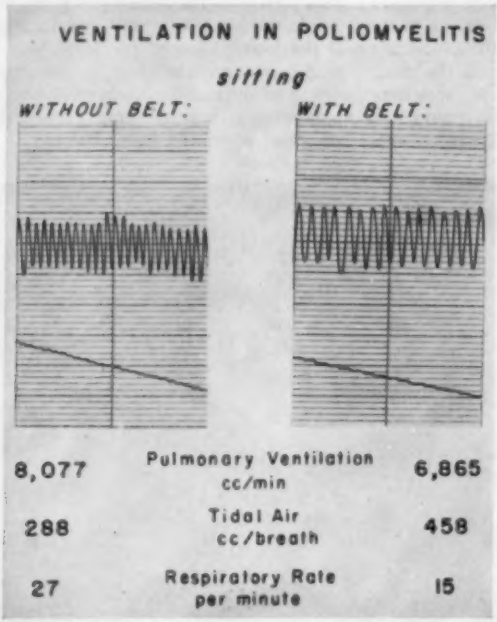


FIG. 5. The patient's pulmonary ventilation record shows a fall from 8,077 c.c. when sitting upright without a lower abdominal belt, to 6,865 c.c. when sitting with belt on. The tidal air is higher with the belt but respiratory rate is markedly decreased, from 27 to 15 per minute.

patient's own observation was an immediate sensation of diminished respiratory effort.

The mean venous pressure recorded before, during and after application of 6.0 cm. positive pressure in the tank was 48, 31 and 50 mm. H_2O, respectively. These observations are summarized in table 2. The fall in venous pressure was similar to that observed in normal subjects exposed to negative intra-mask pressure breathing.[9]

Because of the patient's inability to sleep without the assistance of the rocking bed, a study of his psychologic and physiologic response to complete lung immobilization was conducted, using the lung-immobilizing chamber in a manner similar to that previously reported in patients with pulmonary tuberculosis.[10] He was easily

TABLE II

	Pulmonary Ventilation (Breathing Air) c.c. per minute	Mean Venous Pressure mm. H_2O	Results
Atmospheric Pressure	7,250	48	Accessory intercostal and neck muscle movement
Intra-tank Pressure of 6 cm. H_2O	5,500	31	Lessened dyspnea. Less movement of accessory muscles
Return to Atmospheric Pressure	7,100	50	Return to control state

trained to suspend thoracic and diaphragmatic motion completely during residence in the chamber at alternating pressures of plus 55 to minus 55 mm. Hg, 25 times a minute. A sensation of complete mental and physical relaxation, with complete absence of any conscious effort of breathing, took place. During several of the one-hour periods of ventilation with lung immobilization the patient fell asleep. When the procedure was discontinued he awakened immediately and resumed accessory and thoracic respiration. He invariably described his experiences in the chamber as very pleasant. These subjective findings were accompanied by a fall in pulse rate from 112 to 100 per minute, without change in blood pressure, during periods of one-half to one hour in the chamber.

When the Drinker-type respirator was used to ventilate the patient, no change in heart rate was found. Furthermore, the mental relaxation observed during lung immobilization was not evident. Venous pressure recordings revealed no significant variation of the mean pressure during lung immobilization, but complete absence of respiratory variations of the Statham gauge pressure tracing was observed. This was in marked contrast to the venous pressure rise in the tank-type respirator. With an intra-tank negative pressure of 15 cm. H_2O and a cycling rate of 20, the venous pressure rose from a control of 60 to 91 mm. H_2O; the similarity of venous pressure response between positive intra-mask and negative intra-tank pressure was previously reported.[11] The effects of E.W.N.P., intermittent negative and continuous positive intra-tank pressure and the immobilizing lung chamber on venous pressure are shown in figure 6.

Studies of the effect of eight series of six coughs with E.W.N.P. on the patient's ventilation, vital capacity, blood gases and circulation revealed the following:

The patient's pulmonary ventilation (breathing air) fell from 5,275 c.c. per minute before E.W.N.P. to 4,900 c.c. per minute after E.W.N.P. The vital capacity increased from 580 c.c. to 670 c.c. following the elimination of 30 c.c. of sputum immediately after E.W.N.P. The maximal breathing capacity increased from 12,820 to 14,460 c.c. per minute. Although the patient's oxygen saturation remained unchanged at 98 per cent and his pH at 7.47, his pCO_2 fell from 46.9 to 43.8 mm. Hg. His pulse rate increased from 98 to 112 during E.W.N.P., and 30 seconds after E.W.N.P. fell to 82. No significant change in blood pressure occurred: 108/86 mm. of Hg before E.W.N.P., 112/82 mm. of Hg during E.W.N.P., and 108/76 mm. of Hg after E.W.N.P. The mean venous pressure rose from a control level of 55 mm. H_2O to 66 mm. H_2O during E.W.N.P., and promptly returned to 52 mm. H_2O after E.W.N.P.

During the patient's acute illness in May, 1953, he complained of abdominal pain. The abdomen was markedly distended and he was unable to expel flatus. Serum potassium at that time was 1.6 mEq. Administration of 1 gm. enteric coated potassium chloride four times daily resulted in subsidence of symptoms and return of the serum potassium to a normal level of 4.1 mEq. A similar later episode of sudden

weakness and abdominal pain and distention was accompanied by a fall in serum potassium to 1.6 mEq.; it subsided immediately following the intravenous administration of 60 mEq. of potassium as potassium chloride intravenously. These two episodes were similar to those reported in postoperative patients with low serum potassium [12] and in patients with poliomyelitis.[13, 14]

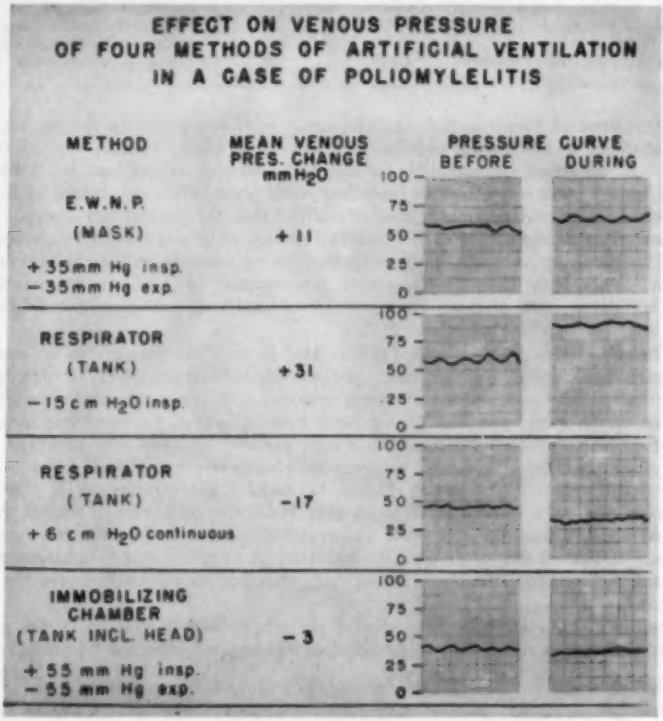


FIG. 6. Exsufflation with negative pressure, using a positive inspiratory pressure of 35 mm. Hg and a negative expiratory pressure of minus 35 mm. Hg, produced a venous pressure rise of 11 mm. H_2O. In the tank type respirator, using a negative inspiratory intratank pressure of minus 15 mm. H_2O, the venous pressure rose 31 mm. H_2O. Using a continuous intratank pressure of plus 6 cm. H_2O, a fall in venous pressure of 17 mm. H_2O occurred. An insignificant fall in venous pressure of 3 mm. H_2O occurred during the patient's residence in the lung immobilizing chamber.

DISCUSSION

Although many of the clinical and physiologic aspects of mechanically induced cough have been described,[1-6] the patient here reported seemed of unusual interest for several reasons. In the first place, the life-saving value of E.W.N.P. was made clear through the relief of obstructive dyspnea as a result of immediate elimination of large amounts of purulent sputum, and,

in a second episode, by the substantial clearing of pulmonary atelectasis after 12 hours' treatment. Later it became evident that blowing secretions from the lungs two or three times daily with E.W.N.P. was required for subjective comfort and for maintenance of such respiratory function as the patient possessed. Finally, continued use of E.W.N.P. was associated with a progressive marked rise in vital capacity, with ability to dispense with the tank respirator during the day and use of the rocking bed at night.

The effect of the application of increased abdominal pressure by an emphysema-type belt was manifested by (1) an instantaneous decrease in the subjective effort of breathing, (2) abandonment of accessory neck muscle and upper intercostal respiration, (3) a decrease of respiratory rate from 27 to 15, and (4) an increase in tidal air with a lowering of the total pulmonary ventilation. The arterial oxygen saturation, pCO_2 and pH were unchanged in this patient after wearing the belt for one hour, even though the minute volume of ventilation was reduced. A similar ventilatory response was induced by a 12 pound sandbag on the abdomen, and, although less marked, by a 6 cm. continuous positive pressure exerted on the body of the patient in the tank respirator and by the head-down position. The behavior of this patient in respect to diffusion of oxygen and carbon dioxide in the presence of a lowering of the total pulmonary ventilation was similar to the changes found in patients with pulmonary emphysema in whom diaphragmatic breathing was induced by the head-down position, in which the viscera elevated the diaphragm, or by increased intra-abdominal pressure by means of a belt or pneumoperitoneum.[4, 5] In cases of pulmonary emphysema, the decrease in pulmonary ventilation in the head-down position was more marked, without, however, the striking increase in tidal air.

In cases of poliomyelitis, a diminished lung, or lung and chest elasticity appears to be frequently present. A less than normal lung volume at various inspiratory pressures has been reported,[7] and, in our studies, smaller than normal expiratory flow-rates with exsufflation were found, as well as smaller tidal volumes at an inspiratory peak pressure of 40 mm. Hg.[4] The increase in residual air volume relative to the total capacity is considered to be physiologically similar to that associated with pulmonary emphysema; limitation of thoracic movements caused by paralysis of muscles used in forced expiration results in an impairment of gas exchange similar to that found in pulmonary emphysema.[8] In this case, increased diaphragmatic excursion on the right side, although of only small extent, was nevertheless of significant aid to breathing when increased pressure was applied to the lower abdomen; the emphysema belt was of value in making up for deficient elastic contraction of the lungs as well as for impairment of accessory expiratory musculature. The weight of 12 pounds performed a similar function, although seven pounds was too little and 17 pounds too great to be helpful. Similar ventilatory responses to this type of belt in other cases indicate that the efficiency of breathing may be improved in other patients with poliomyelitis who manifest impairment of lungs or lung and chest elasticity.

The use of a ptosis pad from a good spinal abdominal corset has also been found to increase diaphragmatic breathing in patients with poliomyelitis and to reduce the use of the accessory muscles of respiration in the neck and upper chest.[15]

A conspicuous effect of E.W.N.P. was the marked excursion of the diaphragm, namely, 6.5 cm., produced by the sudden fall of a plus 40 mm. Hg inspiratory pressure to a minus 40 mm. Hg expiratory pressure. The patient's own maximal diaphragmatic movement at this time was 0.5 cm., in contrast to that measured in a control normal subject, 8.0 cm.

The mental relaxation induced by mechanical pulmonary ventilation without lung movement, generally associated with a rise in serum potassium, has been previously observed in patients treated in the immobilizing lung chamber for pulmonary tuberculosis.[10] In this case, the subjective relief was so marked as to initiate a tendency to sleep or provoke a state of mental relaxation, a response not accomplished by any other form of artificial respiration, such as the tank respirator or rocking bed. The cardiovascular response to total lung immobilization in this patient was a fall in heart rate without change in venous pressure. When the patient was ventilated by the tank respirator, the venous pressure rise was characteristic of other forms of intermittent pressure breathing.[11]

Abdominal distention, reported here in connection with a low serum potassium, has been found during E.W.N.P. on other patients, and is in part attributable to the passage of air past the cardiac sphincter of the stomach, especially when the volume supplied by the device is larger than the patient's inspiratory reserve. Diminution of the inspiratory air flow by means of the volume-regulating valve on the machine very soon abolishes this complication.

The elimination of blood-streaked plugs during the first few mechanical coughs with E.W.N.P. is the rule rather than the exception in the treatment of pulmonary atelectasis. When the obstructing mucous plugs are firmly adherent to the bronchial walls and then peeled away from the mucosa, localized bleeding takes place and streaks the sputum for a short period of time.

Summary

Recently developed methods of aiding the functions of breathing are illustrated in a report of a patient with poliomyelitis. Exsufflation with negative pressure in this case was seen to be a life-saving procedure by eliminating retained secretions from the lungs and thereby relieving obstructive dyspnea; and it was also later responsible for the clearing of pulmonary atelectasis during a period of imminent cardiorespiratory failure. Subsequently, continued use of E.W.N.P. was followed by a threefold increase in vital capacity and ability to dispense with the respirator.

During the patient's maximal cough, diaphragmatic excursion was only

0.5 cm., as contrasted to 6.5 cm. during E.W.N.P. The sudden expiratory ascent of the diaphragm as a result of a total intrapulmonary pressure drop of 80 mm. Hg was manifestly an important factor in eliminating secretions from the bases of the lungs.

The application of an emphysema belt to the lower abdomen relieved the effort of breathing by terminating inspiratory accessory neck muscle and upper intercostal respiration. The respiratory rate was lowered from 27 to 15. The pulmonary ventilation and the tidal air were increased. The increased efficiency of breathing initiated by pressure applied to the lower abdomen was revealed by maintenance of the same arterial oxygen saturation, pCO_2 and pH, with and without the belt, although the minute volume of breathing was substantially reduced. The inability of the diaphragm to ascend during expiration in poliomyelitis may produce physiologic consequences similar to some extent to those seen in pulmonary emphysema.

Residence in the immobilizing lung chamber, which provided mechanical ventilation without lung movement, resulted in a state of marked mental relaxation not obtained by the use of any form of artificial respiration in which ventilation is accomplished by changes in lung volume. The circulatory response to the immobilizing lung chamber was a decrease in pulse rate without change in venous pressure, as contrasted to the characteristic rise in venous pressure due to intermittent pressure breathing in the tank respirator.

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LYMPHOSARCOMA: AN ANALYSIS OF FREQUENCY, DISTRIBUTION AND MORTALITY AT THE UNIVERSITY OF CALIFORNIA HOSPITAL, 1913–1948 *

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This paper is the third of a series of analyses on the frequency, distribution and mortality of patients with neoplastic disease of the lymphatic and hematopoietic tissues seen at the University of California Hospital during the period 1913 to 1948. The reports on granulocytic leukemia and on lymphocytic leukemia have been published,[1, 2] and a report on Hodgkin's disease is in preparation.

The specific purposes of the present study on lymphosarcoma are the same as those stated in previous reports: (1) to analyze statistics relative to age at onset, sex, duration of illness and mortality of patients with lymphosarcoma; (2) to note the possible changes that may have occurred in these statistics during the 35 year period, particularly in regard to the effects of therapy; and (3) to compare the data with similar reports available in the medical literature.

Materials and Methods

All clinical records of patients with lymphosarcoma were personally examined. Cases were included on the basis of definitely established histologic diagnosis of lymphosarcoma. Thus, all cases had at least one relevant biopsy, other surgical specimen, or autopsy.

Follow-up was complete in 206 of 215 patients (96 per cent), of whom 20 were alive on January 1, 1953. The diagnosis was confirmed by autopsy in 77 of the 187 patients known to be dead (41 per cent).

The cases were divided into four major groups. The first group consisted of 95 patients with lymphosarcoma who on admission had the main clinical features of the disease primarily in the peripheral lymph nodes, with or without constitutional symptoms such as fever or anemia. These cases were designated as "lymphadenopathic" lymphosarcoma.

* Received for publication December 22, 1953.
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Supported, in part, by Institutional Grant 43D American Cancer Society, Inc., a special grant from the California Division of the American Cancer Society, funds from the California State Department of Public Health (Contract No. 196), and the Cancer Research Funds of the University of California.

The second group consisted of 52 patients with lymphosarcoma who on admission had the main clinical manifestations of the disease in abdominal or thoracic masses, with or without the presence of peripheral lymph node enlargement. These cases were designated as "visceral lymphosarcoma," and were separated from the lymphadenopathic group because preliminary analysis showed marked difference in the length of survival.

No division was made according to histologic type of the neoplasm, except for the separation of giant follicular lymphoma, and the groups thus include lymphoblastic, lymphocytic, clasmatocytic and reticulum cell sarcomas. Patients with frank lymphocytic leukemia were excluded, but patients who late in the course of the disease or at autopsy were found to have bone marrow invasion were maintained in the groups. It is of course evident that no sharp division can be made between lymphosarcoma and lymphocytic leukemia, and that for statistical purposes such division has to be made on a rather arbitrary basis in individual cases. For this reason, it is important to note that no reduplication of cases included in the previous analysis on lymphocytic leukemia was permitted.

The third group consisted of 44 patients with lymphosarcoma in whom on admission the disease was clinically limited to some specific organ or tissue. These cases, designated as "special-type" lymphosarcoma, included patients with lymphosarcoma of the gastrointestinal tract (18), oropharynx and tonsil (5), skin ("mycosis fungoides") (7), reticulum cell sarcoma of bone (9), and other sites (5). This group was separated from the first two groups because preliminary analysis showed apparently significant differences in survival from the two other groups. Separate group analyses for specific types, histologically or by site, were not undertaken because of the small number of cases in each subdivision.

The fourth group of cases consisted of 24 patients with the diagnosis of giant follicular lymphoma. This group was separated from the others because its progress is known to be different from other types of lymphosarcoma. All these cases were recorded after 1934, since the diagnosis was not made under the lymphomas before that time. It is realized that sharp division is impossible between giant follicular lymphoma and lymphosarcoma. The transitions between the various types are of course well known and well recorded in the medical literature. Undoubtedly some patients in the lymphadenopathic and visceral lymphosarcoma groups initially were cases of giant follicular lymphoma. This is substantiated by the fact that, at autopsy, of six patients with the initial diagnosis of giant follicular lymphoma, in four the diagnosis was changed to lymphosarcoma.

The duration of the disease was determined from apparent clinical onset to death or latest follow-up in January, 1953. When there was a question as to whether the signs or symptoms could have been due to lymphosarcoma, or if such manifestations were not continuous and completely convincing, the date of diagnosis was taken as the date of onset.

Differences between groups were analyzed by accepted statistical methods. Differences were considered "significant" if the probability was 0.05 or less that the difference could have occurred by chance. Some differences were great enough to have probabilities of 0.01 or less.

Analyses

The patients with lymphosarcoma were divided by the four types, and according to three chronologic periods, 1913–1929, 1930–1939, and 1940–1948. These data are presented in table 1. It is seen that the relative distribution of the cases in the lymphadenopathic, visceral and special groups

Table I

Lymphosarcoma. Total Data, University of California Hospital 1913–1948, Inclusive

Date of Admission	1913–29	1930–39	1940–48	Total
Lymphadenopathic Group				
Number of cases	16	39	40	95
Males	13	26	24	63
Females	3	13	16	32
Status Jan. 1, 1953				
Dead	16	36	34	86
Alive	0	0	5	5
Unknown	0	3	1	4
Visceral Group				
Number of cases	8	16	28	52
Males	5	10	17	32
Females	3	6	11	20
Status Jan. 1, 1953				
Dead	8	16	27	51
Alive	0	0	1	1
Unknown	0	0	0	0
Special Group				
Number of cases	6	17	21	44
Males	3	12	11	26
Females	3	5	10	18
Status Jan. 1, 1953				
Dead	5	15	13	33
Alive	0	2	7	9
Unknown	1	0	1	2
Giant Follicular Group				
Number of cases	—	4	20	24
Males	—	2	8	10
Females	—	2	12	14
Status Jan. 1, 1953				
Dead	—	2	14	16
Alive	—	2	3	5
Unknown	—	0	3	3

according to the time periods was approximately the same, and that a random distribution of such cases throughout the three periods could therefore be assumed.

Sex: Of the total 215 cases, 131 were males and 84 were females, a ratio of approximately 1.6 males to 1 female. If the cases of giant follicular lymphoma are excluded, there were 121 males and 70 females, a ratio of 1.7 males to 1 female. When the data are divided into the chronologic periods and the cases of giant follicular lymphoma excluded, there were 69 males and 33 females before 1940, for a ratio of 2 males to 1 female, and 52

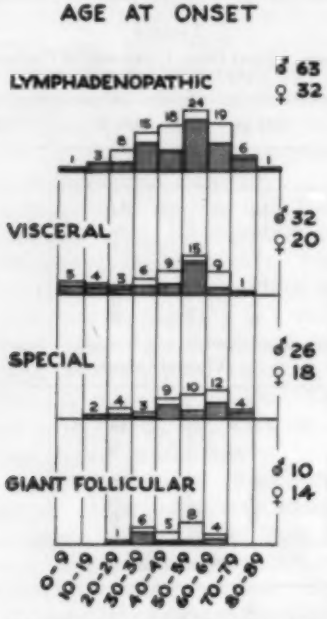


FIG. 1. Age at onset of 215 patients with lymphosarcoma, by clinical type of disease.

males and 37 females after 1940, for a ratio of 1.4 males to 1 female. This shift in sex ratio is not statistically significant, but it is interesting that it is in conformity with similar shifts in the sex ratio observed in the series on chronic granulocytic and chronic lymphocytic leukemia previously reported.

Age at Onset: The ages at onset are given in figure 1. The peak frequency is during the sixth decade (50–59), as in cases of chronic lymphocytic leukemia. The mean age for 191 cases of lymphosarcoma, excluding giant follicular lymphoma, is 48.2 ± 1.2 years.

For the total group of 215 patients, the mean age for males is 47.6 ± 1.5,

and for the females, 49.2 ± 1.6, a difference which is not significant. When the age groups of patients are proportioned to the corresponding age groups of the total hospital admission population, there were more patients with lymphosarcoma whose ages at onset fell into the seventh decade (60–69 years of age). These ratios are presented in figure 2.

Study of the age at onset according to the three chronologic periods, and excluding giant follicular lymphosarcoma, shows that up through 1929, the mean age in 30 cases was 45.0; from 1930 through 1939, the mean age in 72 cases was 46.3; and after 1940, the mean age in 89 cases was 50.8 years. The differences are not statistically significant but, as in chronic granulocytic and lymphocytic leukemia, there is a trend toward a higher mean age during the more recent years. This is probably a reflection of the increasingly higher mean age of the total population.

Analysis of the age at onset according to the four types of lymphosarcoma showed that the mean age for the visceral group was 43.4 ± 2.6; for the lymphadenopathic, 49.2 ± 0.7; for the special group, 51.6 ± 2.3; and for giant follicular lymphoma, 48.5 ± 2.2. The differences fail to show statistical significance, but it is interesting that the younger mean age is recorded for cases with the shorter survival (visceral group).

Survival: Survival in months from clinical onset to death or last follow-up in 215 cases of lymphosarcoma, divided into the four groups, is presented in table 2 and figure 3. Nine patients were lost to follow-up and 20 patients were alive at the last date considered in the analysis (January 1, 1953). The nine patients lost to follow-up are included up to the last

TABLE II

Survival from Onset to Death or Last Follow-Up in Lymphosarcoma, by Clinical Types

Years after Onset	0	1	2	3	4	5	6	7	8	9	10
Lymphadenopathic Group											
No. cases alive	95	66	47	37	29	22	19	14	11	7	4
Per cent alive	100	69.5	49.5	38.9	30.5	23.2	20.0	14.7	11.6	7.4	4.2
Standard error of per cent ±	—	4.7	5.1	5.0	4.7	4.3	4.1	3.6	3.3	2.7	2.1
Visceral Group											
No. cases alive	52	28	12	7	3	1	1	1	1	0	—
Per cent alive	100	53.8	23.1	13.5	5.8	1.9	1.9	1.9	1.9	—	—
Standard error of per cent ±	—	6.9	5.8	4.7	3.2	1.9	1.9	1.9	1.9	—	—
Special-type Group											
No. cases alive	44	34	28	25	22	17	13	9	8	7	7
Per cent alive	100	77.3	63.6	56.8	50.0	38.6	29.5	20.5	18.2	15.9	15.9
Standard error of per cent ±	—	6.3	7.2	7.5	7.5	7.3	6.9	6.1	5.8	5.5	5.5
Giant Follicular Group											
No. cases alive	24	24	20	15	14	11	9	6	3	2	2
Per cent alive	100	100	83.3	62.5	58.3	45.8	37.5	25.0	12.5	8.3	8.3
Standard error of per cent ±	—	—	7.6	9.9	10.1	10.2	9.9	8.8	6.7	5.6	5.6

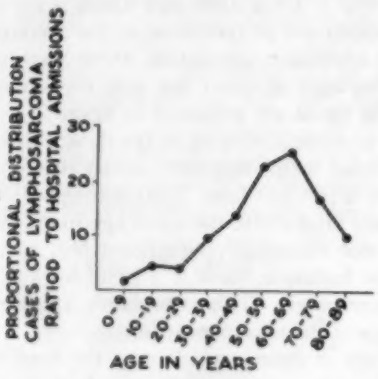


FIG. 2. Distribution of cases of lymphosarcoma, against the percentile distribution of admissions, by age, to the University of California Hospital.

month the patients were known to be alive. Since the exclusion of these patients does not affect the mortality curve to a significant degree, subsequent analyses are based on the total 215 patients. Although it is evident that not all patients after 1943 could be followed for the full 10 year period, the drop-out of later years does not affect the mortality curve to a significant degree. Therefore, the total number of patients is retained as the denominator for the determination of the per cent of patients surviving.

There are significant differences in survival between the groups designated as the lymphadenopathic and the visceral types of lymphosarcoma, at two, three, four and five years after onset. There are significant differences in survival between the groups designated as the lymphadenopathic and the special types of lymphosarcoma at three and four years after onset. The differences between the "special type" lymphosarcoma and giant follicular

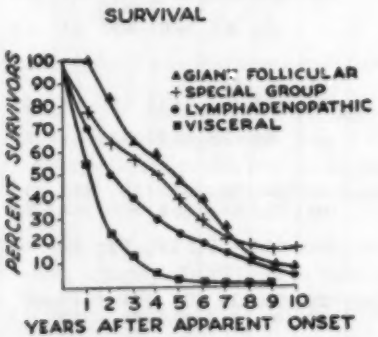


FIG. 3. Survival in 215 patients with lymphosarcoma, from clinical onset, by clinical type of disease.

lymphoma are not significant, but the groups are represented by relatively small numbers of cases.

At five years after onset, the survival in all 215 patients was 23.7 ± 2.9 per cent. This includes the survival of 2 per cent of the patients with visceral lymphosarcoma, 23 per cent of the patients with lymphadenopathic lymphosarcoma, 39 per cent of the patients with special types of lymphosarcoma and 46 per cent of the patients with giant follicular lymphoma. The five-year survival of 147 patients comprising the lymphadenopathic and visceral groups was 15.6 ± 3.0 per cent.

There were no significant differences in survival between males and females, although in each group the percentage of females surviving was higher. Thus, in the lymphadenopathic group the survival at three, four and five years of 63 males was 33, 25 and 22 per cent, respectively; whereas among 32 females it was 50, 41 and 25 per cent, respectively. In the visceral lymphosarcoma group, three of 32 males, or 9.4 per cent, survived for three years; whereas four of 20 females, or 20 per cent, were alive at that interval.

Age at onset was shown to have an effect upon survival in the lymphadenopathic group, in that survival at three and four years was better at a statistically significant level among patients under 45 years of age. Of 33 cases under 45 years of age, 51 per cent survived for four years; the four-year survival among 25 patients 45 to 54 years of age was 24 per cent; and among 37 cases 55 years and over, it was 16 per cent. No differences relative to age were evident in the visceral, special or giant follicular groups, but the numbers of cases in each instance were insufficient for adequate analysis.

Duration of Illness: The mean duration of illness by the four groups of lymphosarcoma, and excluding cases who lived for over 10 years, was 16.9 ± 2.4 months in 52 patients with visceral lymphosarcoma, 33.9 ± 3.3 in 91 patients with lymphadenopathic lymphosarcoma, 37.2 ± 4.7 in 37 patients with special types of lymphosarcoma, and 53.3 ± 5.8 months in 22 patients with giant follicular lymphosarcoma. The median duration, for the same four groups, was approximately 13, 22, 34 and 52 months, respectively.

Effect of Treatment: No attempt was made to analyze treatment in detail, because no definite and consistent policy was followed for any particular group or with any treatment method. Of the total 215 patients, 174 received some form of radiation during the course of the disease. Of these, 136 were treated only with x-ray, varying from a few palliative administrations to tissue doses of 2000 r and over. Radiophosphorus or radium was used in addition to x-ray in 14 cases; potassium arsenite, urethane or nitrogen mustard was used in addition to x-ray in 12 cases. Surgery, with subsequent radiation therapy, was employed in 11 cases.

Only 41 patients received no radiation therapy, or such therapy was not recorded in the clinical record. Of these, nine were treated surgically, two

TABLE III

Survival in Lymphosarcoma, According to Major Types of Treatment

Years after Onset	0	1	2	3	4	5
Lymphadenopathic						
Radiation only	65	45	32	27	22	18
Radiation plus other*	15	11	8	8	7	4
No radiation	15	10	7	2	—	—
Visceral						
Radiation only	38	20	9	5	1	1
Radiation plus other*	7	6	2	1	1	—
No radiation	7	2	1	1	1	—
Special Types						
Radiation only	18	15	13	11	8	7
Radiation plus other†	6	6	5	5	5	4
Surgery plus radiation	8	6	4	3	3	2
Surgery only	7	5	5	5	5	3
No radiation or surgery	5	2	1	1	1	0
Giant Follicular						
Radiation only	15	15	14	10	9	7
Radiation plus other*	2	2	2	1	1	0
No radiation	7	7	7	4	4	4

* Surgery, potassium arsenite, nitrogen mustard or urethane.
† Potassium arsenite or nitrogen mustard.

received only nitrogen mustard, and one only potassium arsenite; no treatment except supportive measures such as transfusions and analgesics was recorded in 29 cases (table 3).

It is of interest to compare the survival of patients seen before 1940 and those seen after that date. In the lymphadenopathic group, the survival at one, two, three, four and five years among 55 patients seen between 1913 and 1939 was 69, 47, 33, 24 and 18 per cent, respectively; among 40 patients seen after 1940, it was 72, 55, 50, 42 and 32 per cent, respectively. The difference at four years is the greatest, yet fails to show statistical significance at the 5 per cent level. The division of the 52 cases of visceral lymphosarcoma and of 44 cases of special-type lymphosarcoma by these two periods shows almost identical survivals in each instance.

Among the total 215 patients are 10 patients who may be considered as "cured" in the sense that they were clinically free of disease at five to over 20 years following treatment. Eight of the patients were in the special-type group of 44 patients and included the following: two cases with lymphosarcoma of the stomach, and one each with lymphosarcoma of the small intestine, rectum, tonsil, lung and soft tissue of the cheek and of the chest wall. Two of the patients, one with lymphosarcoma of the small intestine and the other of the lung, were treated by radical surgery only. Three patients, one with lymphosarcoma of the rectum and one each of the soft tissue of the chest wall and of the cheek, were treated by radiation only. In three remaining patients, treatment consisted of both surgical removal and

postoperative radiation. Among 95 patients with lymphadenopathic type of lymphosarcoma, two remain apparently free of disease seven and 11 years later; one had lymphosarcoma of the axillary lymph nodes, treated by radiation only, and the other had cervical involvement, treated by radical neck dissection and radiation. Among 24 patients with giant follicular lymphoma, two patients are living 20 years after diagnosis and treatment by radiation, but with evidence of persistent disease. No patients were recorded as free of disease in the visceral type of lymphosarcoma.

It is difficult not to conclude that there was salvage of approximately 5 per cent of all lymphosarcoma cases as a result of treatment by radiation and surgery. It is also evident that in the total series, such salvage could hardly be expected to be reflected in statistically significant differences, particularly when selection of cases as an essential in medical management is so greatly involved.

Even assuming that all the 10 patients are cured in the sense of permanent eradication of the disease, the 4.6 per cent five year figure should be compared with the total survival of 23.6 per cent of the 215 patients at five years after onset. Two conclusions are possible. The first is that the span of life is prolonged by treatment even in cases in whom such treatment does not eradicate the disease. The second is that, of the 23.6 per cent survival, all but 4.6 per cent, or 19 per cent, represents the natural duration of the disease. The data are inadequate to establish which of the two contentions is correct.

Probably of more importance than establishing whether the life span is prolonged in generalized lymphosarcoma by radiation or other therapy is the fact that a small percentage of the cases can be maintained clinically free of disease for periods of from five to 20 years. These cases, without exception, appear to be localized to some organ or site, and are eradicated by adequate radiation, or by complete surgical excision. If these conclusions are accepted, it follows that at least in some instances lymphosarcoma is a localized neoplasm, and that earlier detection and adequate treatment of the disease will increase to some degree the number of cases that remain clinically well for many years.

Discussion

As in the case of the literature on the leukemias, it is an occasion of some surprise to find so few papers that systematically present what is apparently the total, unselected data of an institution regarding cases of lymphosarcoma. Table 4 summarizes six such reports from three localities, although in the work of Minot and Isaacs [4] no distinction is made between lymphosarcoma and Hodgkin's disease. The reports of Sugerbaker and Craver [5] and Craver [6] are the only ones in which comparative results from one institution during two chronologic periods are available.

TABLE IV

Comparative Data on Lymphosarcoma

Author	Region	Dates	No. Cases	Per Cent	Age Onset Years	Survival Mean Months	5-Year Survival Per Cent
Desjardins and Ford[3]	Minnesota	1915–20	102	81	40.7	29.5	11.0
Minot and Isaacs[4*]	Boston	1901–25	401	80	36.7	30.8†	12.0
Sugerbaker and Craver[5]	New York	1918–33	132	70	45.1	—	15.9
Stout[6]	New York	1915–35	218	—	—	—	16.5
Gall and Mallory[7]	Boston	1917–36	347	74	45	—	15.2
Craver[8]	New York	1930–40	308	—	—	—	26.3

* Including Hodgkin's, and only dead patients analyzed.
† Not counting patients surviving over 10 years (seven cases).

Table 4 indicates several findings that apparently coincide with some of the indications of the present report. It is to be noted that the percentage of males in the earlier report of Desjardins and Ford [3] was 80; two later papers state that 70 and 74 per cent of the cases were males, suggesting a greater proportion of females among the more recent series of lymphosarcoma. The mean age at onset, given as 41 years by Desjardins and Ford [3] on data up to 1920, is stated to be 45 years in the more recent reports of Sugerbaker and Craver [5] and of Gall and Mallory.[7] These findings are in conformity with the higher mean age found during the more recent cases of the present report. It is of interest that Videbaek's [9] recent paper from Denmark indicates that 29 of 55 cases of lymphosarcoma were females, and that the average age was 50.

It is unfortunate that lymphosarcoma as an entity has been tabulated separately in the national mortality statistics only since 1949.[10] Thus, it cannot be determined from the presently available data whether these shifts in the sex ratio and in the mean age represent true changes in the population developing the disease, or merely reflect parallel changes in the total population of the locality in which such cases occur.

Table 4 also suggests that the five year survival of patients with lymphosarcoma has risen between 1915 to 1940, from 11 per cent before 1920, to 16 per cent by 1935, and to over 25 per cent by 1940.

One of the important considerations that enter into the evaluation of the survival figures is whether the same types of patients are included in each series. This can hardly be the case when series reported before 1930 and after 1930 are compared. Lymphosarcoma as a neoplastic entity was established by Kundrat [11] in 1893. In 1926, however, Minot and Isaacs [4] still grouped Hodgkin's disease and some related conditions under the general designation of lymphoblastoma or malignant lymphoma. A diametrically opposite concept, of dividing the malignant lymphomas into a half-dozen histologic types, was developed by Gall and Mallory.[7]

The review of the earlier papers of Desjardins and Ford [3] and of Minot and Isaacs [4] indicates that almost all, if not all, of their patients had general-

ized disease. The concept of localized lymphoma became accepted at a later date, through such reports as those of Stout.[6] Moreover, a number of types of malignant lymphoma simply were not recognized before 1930. This is the case in giant follicular lymphoma [12] and reticulum cell sarcoma of bone,[13] two somewhat different processes typified by long survival of the patients.

Thus, in comparing the figures of Desjardins and Ford,[3] of 11 per cent five year survival in 102 cases, with Stout's [6] figure of 16.5 per cent in 218 cases, it should be emphasized that the latter includes 61 patients with lymphoma of the gastrointestinal tract, skin, orbit and nasopharynx, in whom the five year survival was 25 per cent. If these patients are considered separately, the survival of the remaining 157 patients was 13.4 per cent, a figure very close to that reported by Desjardins and Ford.[3]

Whether irradiation with x-ray has an effect upon the length of survival of generalized lymphosarcoma cannot be established from the data presented here, since no comparable group that did not receive such treatment is available. Minot and Isaacs [4] in 1926 stated that the average duration of life in 238 patients treated with roentgen-rays or radium was 34.6 months, whereas among 163 that did not receive such treatment it was 29.4 months. This difference is not statistically significant, and the authors recognized that the groups were not strictly comparable, since patients with more acute forms of lymphoblastoma "probably soon become so ill that they are unable to reach a hospital where irradiation can be given; or it may be believed that their condition is so precarious that they are not referred for such therapy."

Craver [8] compared the five year survival figures in patients with lymphosarcoma seen at the Memorial Hospital in New York from 1918 through 1933, with the patients seen between 1930 through 1940. The former group was reported in detail by Sugerbaker and Craver [5] and consisted of 132 patients, of whom 15.9 per cent were alive at five years. The latter group, of 308 patients, of whom 26.3 per cent were alive at five years, is indicated by a summary statement only, and presumably includes some patients of the former series, since the periods overlap. If the two groups are comparable, the difference between 15.9 per cent and 26.3 per cent is significant at the 2 per cent level and would indicate improvement in survival, possibly due to the improvement in medical management of the condition, or a greater proportion of localized disease.

It should be emphasized that the demonstration or lack of demonstration that radiation or other forms of therapy might have an effect on the duration of the disease is not the only criterion for the use or non-use of such measures. The benefits to individual patients, in terms of more comfortable life, amelioration of symptoms and medical interest, dictate their use. Despite the many years of use of x-rays in the treatment of lymphomas, the possibilities regarding dosage, frequency of treatment, localized or general treatment, and combination with various drugs still have not been systematically explored. It should also be remembered that in the total clinical

management of patients with disseminated lymphoma, many measures may be used, including blood transfusions, antibiotics and supportive drugs. The sum-total effects of such general measures, and the meticulous consideration and treatment of complications with entirely unrelated diseases, may be as important as the use or non-use of any one more "specific" modality of treatment.

This discussion, primarily regarding the usual disseminated form of the disease, obviously does not apply to the rarer cases in whom the disease is apparently localized, who should be treated by the full measures of surgery and/or radiation. The reports of Stout,[6] Craver,[8] Hellwig,[14] Holmes and Schulz,[15] Catlin [16] and the present findings certainly demonstrate that a small proportion of such cases is clinically "curable" for many years.

Summary

Statistics are presented regarding the age at onset, sex, duration of illness and mortality of 215 patients with lymphosarcoma seen at the University of California Hospital, 1913 to 1948, inclusive. The cases were divided into four groups, as follows: 95 patients with lymphosarcoma primarily manifested by peripheral lymphadenopathy; 52 patients with visceral lymphosarcoma; 44 patients with special types of lymphosarcoma such as of the stomach, intestines, tonsil, bone or skin; and 24 patients with giant follicular lymphoma. The data are compared with six similar reports in the literature.

The sex distribution suggests a shift toward more females, and the age distribution suggests a higher mean age during recent years, but the differences are not significant statistically.

The mean duration of illness in months for cases with lymphadenopathic lymphosarcoma was 34, for visceral lymphosarcoma 17, for special types of lymphosarcoma 37, and for giant follicular lymphoma 53. The five year survival of all 215 patients was 24 per cent, varying from 2 per cent in visceral lymphosarcoma to 46 per cent in giant follicular lymphoma. Ten patients remained free of clinical evidence of disease at from five to 21 years after treatment with surgery or radiation; of these, eight had lymphosarcoma of the stomach, intestines, tonsil, lung or soft tissue, and two had lymphosarcoma apparently limited to cervical or axillary lymph nodes.

No significant differences in survival were found between chronologic periods of the study (1913–29, 1930–39 and 1940–48), or by sex. In the lymphadenopathic group, survival was significantly better in patients under 45 years than in patients over 45 years of age.

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THE CLINICAL PICTURE OF PULMONARY STENOSIS (WITHOUT VENTRICULAR SEPTAL DEFECT)*

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Pulmonary stenosis is an extremely common congenital lesion. Surgical repair is possible, and accurate clinical recognition is therefore imperative. After establishing the diagnosis in 20 cases by cardiac catheterization, we have attempted to correlate our clinical findings in an effort to draw an accurate clinical picture. The following generalizations are significant:

I. *Body Type and Facies.* Normal physical habitus was the rule in our group. In several cases the growth and development have been reported to be retarded; British authors [1] in particular have commented upon the moon face and blotched skin which seem to characterize the patient with pulmonary stenosis. Two of our patients could be classified as moonfaced, and two demonstrated blotched facies; the other 16 had "normal" facies. The particular face did not, therefore, impress us. Retardation of growth was not characteristic either.

II. *Auscultation.* The presence of a harsh systolic murmur along the left sternal border, varying from grade II to grade VI, is more likely to be due to pulmonary stenosis than to ventricular septal defect. It is very unlikely to be due to an auricular septal defect. The murmur is usually maximal at the second and third left interspaces. It has been stated that classically the pulmonary second sound is diminished or absent. This is true in the presence of severe stenosis. However, in the presence of moderate or mild stenosis the pulmonary second sound may be reduplicated and louder than the aortic second sound (seven of our 20). We are unable to correlate the presence of a pulmonary artery diastolic pressure elevation with the intensity of P_2. Too much significance has been attributed to the differential value of the pulmonary second sound. The loudness of the pulmonary systolic murmur does not correlate well with the severity of the stenosis. Case 8 (table 2), in whom the right ventricular pressure was 75/0, had a grade VI murmur, while in cases 16, 17 and 19, with right ventricular pressures of 170/0 or more, only a grade III or grade IV systolic murmur was noted. A pulmonary diastolic murmur is also present in an occasional patient (three of our 20). The presence of such a diastolic murmur is difficult to explain. It does not mean a failing circulation; no special features

* Received for publication September 30, 1953. (Presented before the Kansas Regional Meeting of the American College of Physicians, 1953.)

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indicating incipient difficulty were associated with these three patients. In only one (case 4) was there an elevation of the diastolic pulmonary artery pressure, which might suggest a cause for a regurgitant murmur. The reason for the elevated diastolic pressure was not apparent. It is interesting to note that in case 3 the diastolic murmur developed during two years of observation and was associated with increasing poststenotic dilatation.

TABLE I

Fluoroscopic and Roentgenologic Findings

Case No.	Pressure in mm. Hg		Main Pulmonary Artery		RPA & LPA		R. V.	Pulmonary
	R. V.	P. A.	Poststenotic Dilatation	Pulmonary Segment	Size	Pulsation	Enlargement	Field
1	34/0	24/6	Absent	Normal	N	N	Absent	N
2	40/0	12 mean	2+	Convex	N	Slightly decreased	1+	N
3	40/0	15/5	3+	Convex	N	N	1+	N
4	40/0	15/13	2+	Convex	1	N	1+	N
5	55/0	20/6	1+	Convex	N	N	Absent	N
6	62/0	18/5	2+	Convex	N	N	Absent	N
7	65/0	20/5	Absent	Normal	N	N	2+	N
8	75/0	10/2	Absent	Concave	N	N	2+	N
9	84/0	20/8	3+	Convex	2	N	Absent	N
10	85/0	12/5	1+	Convex	N	N	1–2+	Clear
11	105/0	22/2	Absent	Normal	N	N	1+	N
12	110/0	22/8	Absent	Normal	N	N	3+	Clear
13	120/0	15 mean	Absent	Normal	N	N	3+	N
14	140/5	14 mean	Absent	Concave	N	N	4+	N
15	163/22	20/8	3+	Convex	N	N	2+	Clear
16	170/0	15 mean	Absent	Concave	2	N	4+	Clear
17	175/0	8 mean	Absent	Concave	N	N	3+	Clear
18	40/0	28/12	Absent	Normal	N	N	1+	Clear
19	180/0	14/6	Absent	Normal	N	N	3+	N
20	175/0	28/8	2+	Convex	Slightly increased	Slightly increased	1+	N

Degree of poststenotic dilatation: from 1 to 4+
Degree of right ventricular enlargement: from 1 to 4+
Grade of pulmonary artery: from 1 to 4+
N means normal.

III. *Electrocardiogram.* The electrocardiographic pattern varies from normal to marked right ventricular hypertrophy. In general, the electrocardiogram correlates well with the right ventricular pressure, but exceptions are frequent. For example, patients with right ventricular pressures of 40/5 (case 4), 62/0 (case 6), 105/0 (case 11) had similar electrocardiograms. The P waves are occasionally tall and peaked in severe cases (cases 13 and 14). A changing electrocardiographic pattern, as evidenced by increasingly widened QRS complexes and increasing amplitude of the P waves, is probably good evidence of impending difficulty and is adequate indication for a pulmonary valvotomy. Although right ventricular hypertrophy pattern is usually present if the pressure in the right ventricle is greater than 60 mm. Hg, this is not a constant finding. In our series of

TABLE II

Clinical and Cardiac Catheterization Findings in 20 Cases of Pulmonary Stenosis

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total
R. A. mm. Hg	2	—	2	8	7/3	4	5	5	15	—	4	4	10	5	—	3	5		14/6	5	
R. V. mm. Hg	34/0 24/0	40/0	40/0	40/5	55/0	62/0	65/0 50/0 22/0	75/0	84/0	85/0	105/0	110/0	120/0	140/0	163/22	170/0 110/0	175/0	40/0	180/0	175/0	
P. A. mm. Hg	24/6	12	15/5	15/13	20/6	18/5	20/10	16/4	20/8	12/5	22/2	22/8	15	14	20/8	15	8	28/12	18/6	28/8	
Systolic Murmur-Grade Location of Max. Intensity of Sys. Murmur i.c.s.	2 2	3 2	4+ 2	3+ 2	2+ 2	4 2	4 2 3	6 2	4 2	4 2	4+ 3	4 2	3 2	3+ 2	4+ 2	3 4	4 4	2 2	3 3	4+ 1	20
Systolic Thrill			++			+	++	++++	+		+	+		+	+		++			+	11
Diastolic Murmur			+	+		+															3
$A_2 > P_2$							+	+	+			+	+		+		+				7
$P_2 > A_2$	+	+	+	+	+	+					+										7
P_2 Split		+	+	+	+	+					+							+			7
P_2 Grade	1	N	1+	1+	1+	+					N							N			6
P_2 Diminished								+	+			+	+		+		+				5
P_2 Absent										+				+		+			+	+	

20 cases we have three patients with normal electrocardiograms, 14 of right ventricular hypertrophy, and three of complete right bundle branch block. The electrocardiographic changes in 17 cases are presented in figure 1 (A and B).

IV. *Fluoroscopy and X-ray.* Classically, the lung fields are said to be "clear" and "ischemic." This is probably true in severe stenosis; however, in general the lung markings would be hard to differentiate from normal. There is considerable value in noting that the mid-lung pulmonary arteries never "dance," although the main pulmonary segment may be very prominent and active. This discrepancy in activity between the "post stenotic dilatation of the main pulmonary artery" and its branches is clinically true and useful. The main pulmonary segment may be very large and active in valvular pulmonary stenosis. If the obstruction is in the ventricle (infundibular), the main pulmonary segment usually appears normal.

X-ray and fluoroscopic findings in pulmonary stenosis can be summarized as follows:

1. *Disproportion of degree of systolic pulsation between the main pulmonary artery (MPA) and its branches:* The markedly increased systolic pulsation of the main pulmonary artery is seen as a contrast to the normal or decreased pulsation in the right and left pulmonary artery (particularly the right pulmonary artery).

2. *Presence of poststenotic dilatation:* The prominence of the pulmonary artery beyond the stenotic portion in pulmonary valvular stenosis has been well described.[2, 3, 4] It is probably due to the Venturi effect.[5] Such an effect is caused by the conversion of more *pressure* energy to *velocity* energy at the area of constriction, and reconversion of velocity energy to pressure energy as the stream bed widens. In the case of infundibular pulmonary stenosis, the pulmonary artery is usually normal.

3. *Right ventricular or right auricular enlargement:* The right ventricular enlargement is relatively easy to demonstrate. However, the demonstration of slight right auricular enlargement is difficult.

4. *Pulmonary fields:* Most of the severe cases show clear pulmonary fields. Because of compensating bronchial circulation and varying x-ray technic, the pulmonary fields may appear quite normal. In mild or moderate cases, the "clearness" of the lung fields is of no help in making the diagnosis. Figure 2 illustrates the chest films of 17 cases of pulmonary stenosis; note the marked variation in intensity of the lung fields and general contour of the heart. The x-ray and fluoroscopic findings in these 20 cases are tabulated in table 1.

In pure pulmonary valvular stenosis, poststenotic dilatation is rather common, although it may sometimes be absent. Occasionally the right ventricle was so much enlarged that the poststenotic dilatation was obscured by the protruding ventricle (cases 7, 8, 11, 12, 13, 14, 16, 17, 18, 19). Disproportional degree of pulsation between the main pulmonary segment

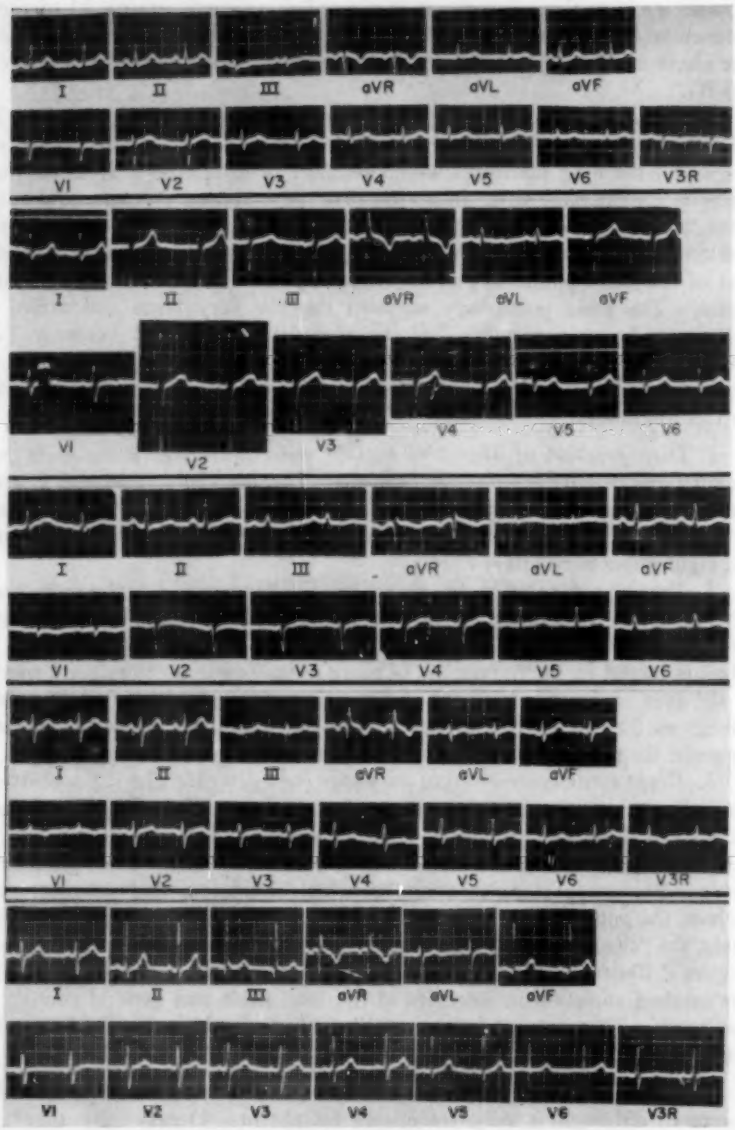


FIG. 1. Electrocardiographic changes in 17 cases of pulmonary stenosis. These electrocardiograms shown in the four sections of figure 1 are arranged consecutively, beginning with case 1 and ending with case 17. The chest leads are all recorded at one-half standard.

and the right and left branches is apparent in most cases of valvular pulmonary stenosis. The infundibular type usually showed a normal main pulmonary segment without poststenotic dilatation, as in cases 1, 7 and 16. Occasionally a small bulging of the lower portion of the pulmonary outflow tract in the right anterior oblique position indicates an enlarged infundibular chamber. Certainly there was no correlation between the degree of poststenotic dilatation and elevation of right ventricular hypertension as mentioned by Abrahams and Wood.[1] In conclusion, the poststenotic dilatation, disproportional pulsation between MPA and the right and left branches, and

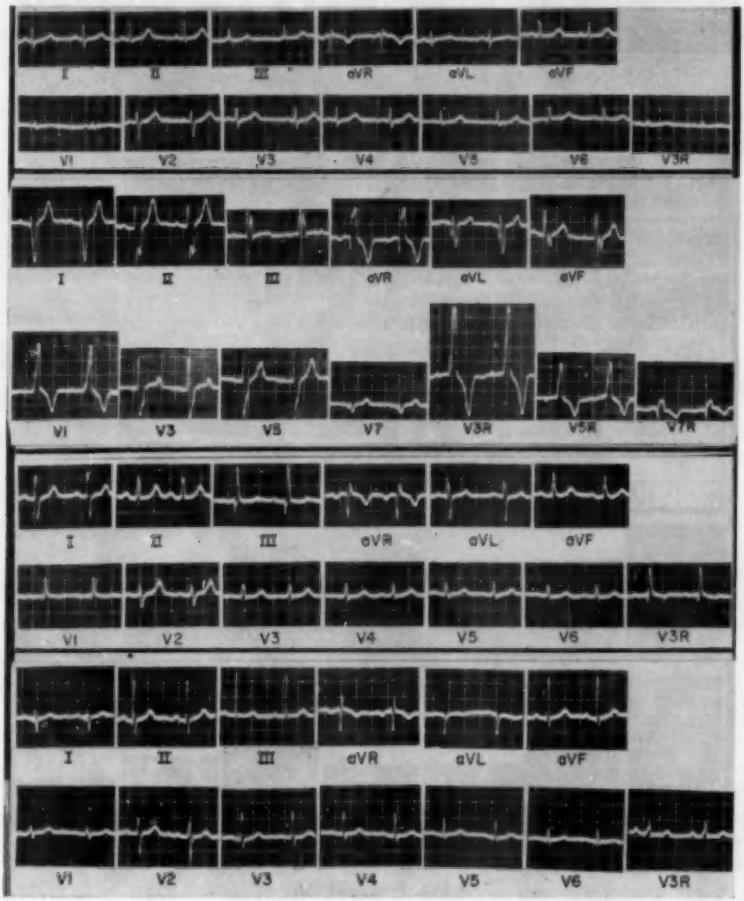


FIG. 1—*Continued.*

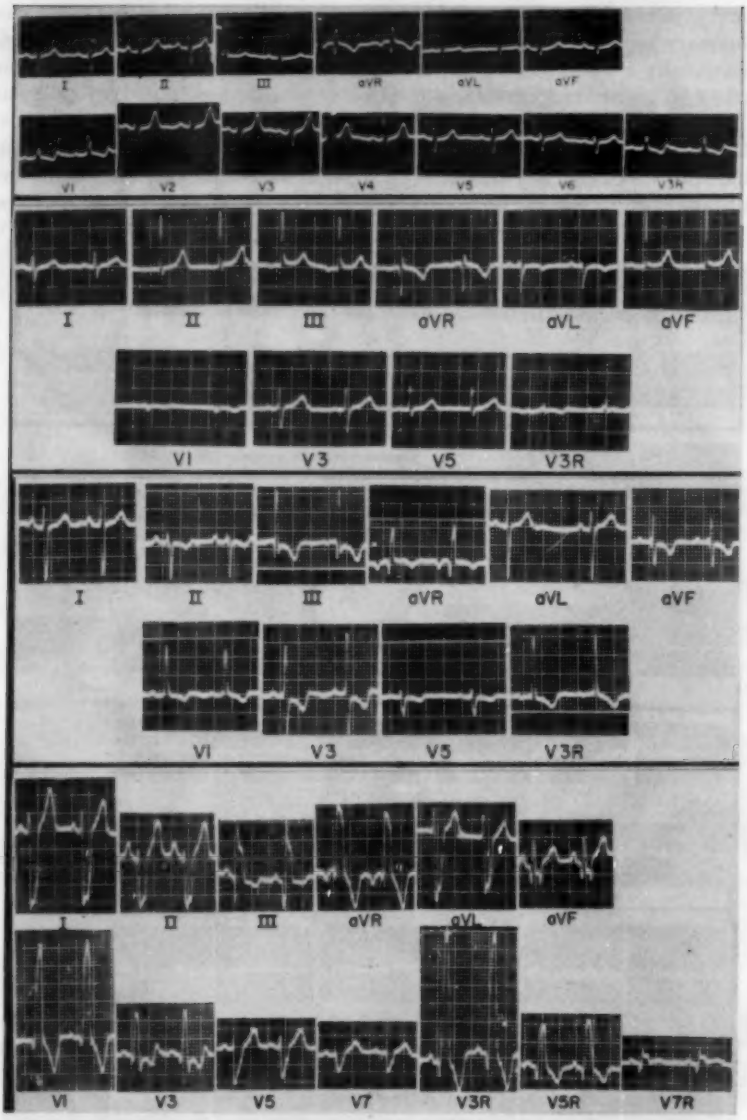


FIG. 1—*Continued.*

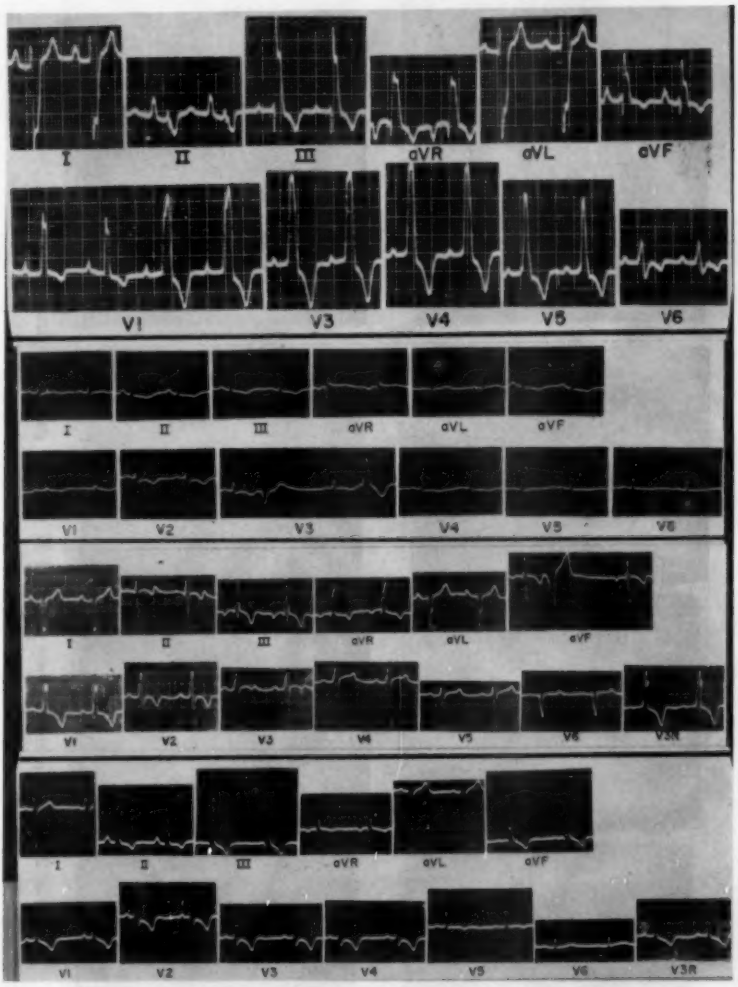


FIG. 1—*Continued.*

right ventricular enlargement are the most common findings in this series of pulmonary valvular stenosis.

V. *Cardiac Catheterization.* Cardiac catheterization studies in pulmonary stenosis have been well described [1, 6, 7, 8, 9] and, in general, indicate a higher pressure in the right ventricle and lower pressure in the pulmonary artery. The systolic pressure in normal hearts should be the same on either side of

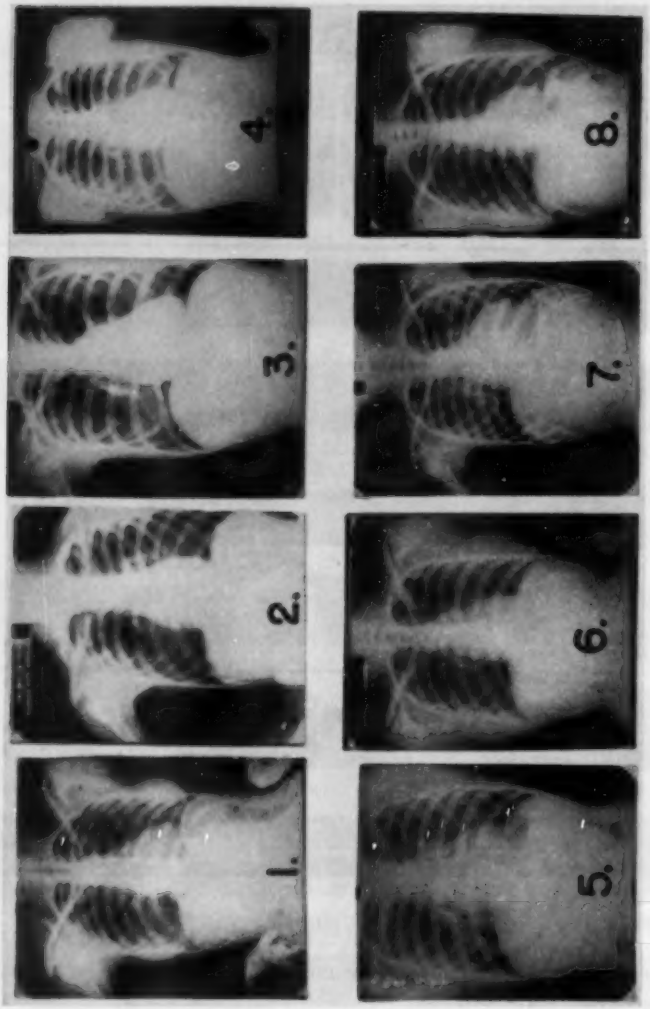


FIG. 2. Antero-posterior chest x-ray of 17 cases of pulmonary stenosis.

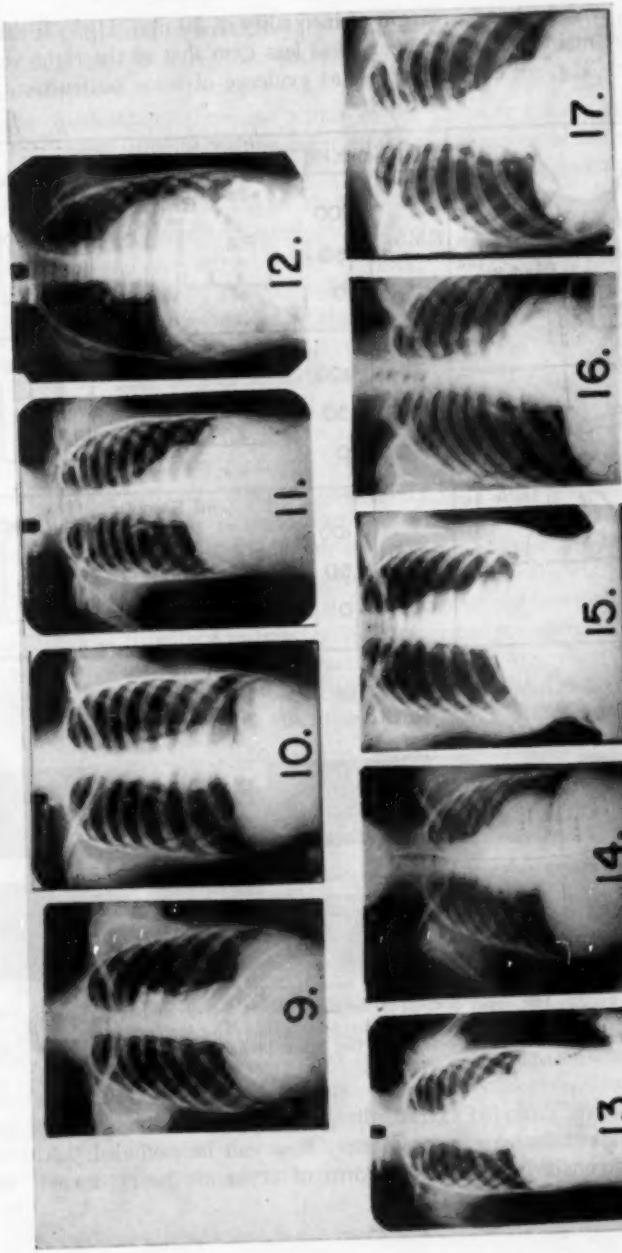


FIG. 2—*Continued.*

the valve, with perhaps a margin of inequality of 10 mm. Hg. If the pressure in the main pulmonary artery was less than that of the right ventricle by 10 mm. Hg, we considered this as evidence of some obstruction at the

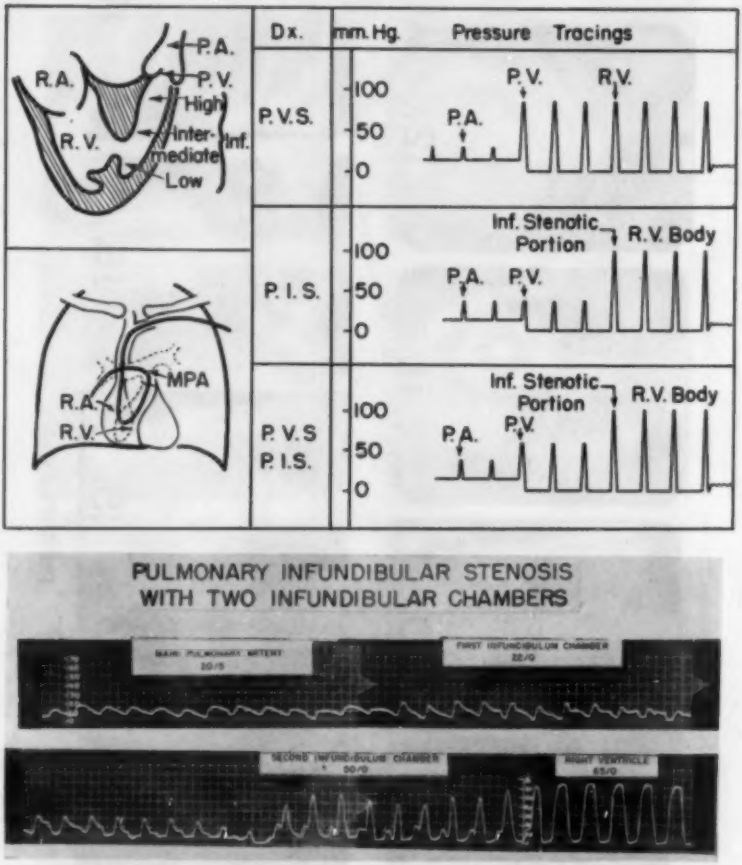


FIG. 3. *Case 7.* The upper portion of the chart shows a diagrammatical sketch of three typical types of pressure tracings in pulmonary stenosis. The lower portion of the chart shows a case of pulmonary stenosis with two infundibular chambers. P.V.S. = valvular stenosis. P.I.S. = infundibular stenosis.

pulmonary valve, provided extracardiac compression of the artery or some cause for marked increase in pulmonary flow can be excluded. Although pulmonary stenosis is generally a form of acyanotic heart disease, some

decrease in peripheral arterial oxygen saturation is not uncommon. This is frequently due to a right-to-left shunt from the right to left auricle through either a patent foramen ovale or an auricular septal defect.

Figure 3 illustrates three variations of the pressure curves in the pulmonary stenosis: valvular, infundibular, and a combination of both valvular and infundibular types. The recognition and differentiation of these types become important when surgery is considered. In simple infundibular pulmonary stenosis there is a pressure difference between the body of the right ventricle and the infundibular chamber only during systole and no pressure difference during diastole. However, in complicated cases of the infundibular type, two infundibular chambers may be demonstrated, as in case 7 in figure 3. In order to obtain the pressure curve of infundibular stenosis, the catheter should be withdrawn very slowly and the tip of the catheter, as well as the pressure curve, observed carefully. The diagnosis of the infundibular stenosis will then rarely be missed. The tracings may need to be obtained at varying speeds with several repeated passages through the valve. This will offer a better opportunity to pick up the mild changes through the infundibular stenotic portion. Figure 4 illustrates a case of asymptomatic pulmonary infundibular stenosis, and figure 2, a case of pulmonary infundibular stenosis with two infundibular chambers. Figure 5 (case 16) shows a combined type of stenosis. In severe cases of pulmonary stenosis there is usually a narrow pulmonary pulse pressure, although the mean pulmonary pressure may be normal. Extremely high right ventricular pressures such as 233/12,[10] 260/5,[1] 240/0 [6] and 260/0 [11] have been reported.

VI. *Differential Diagnosis Between Valvular and Infundibular Pulmonary Stenosis.* The following table lists the essential points for differentiation between the pure valvular and the infundibular types of pulmonary stenosis:

Differential Remark	Valvular Type	Infundibular Type
Incidence[1,2,5,9,13]	82%	18%
Location of systolic murmur and thrill	Usually at pulmonic area	Usually lower
Diastolic murmur	May be present	Usually absent
Poststenotic dilatation	Usually present	Usually absent
Bulging of lower left midsegment (R.O.A.)	Usually absent	Usually present
Prominent pulsation of M.P.A. Normal or decreased pulsation of R.P.A. or L.P.A.	Usually present	Usually absent
Cardiac catheterization	Valvular type of pressure tracing	Infundibular type of pressure tracing
Angiocardiography	Demonstration of poststenotic dilatation	Demonstration of narrow infundibular chamber

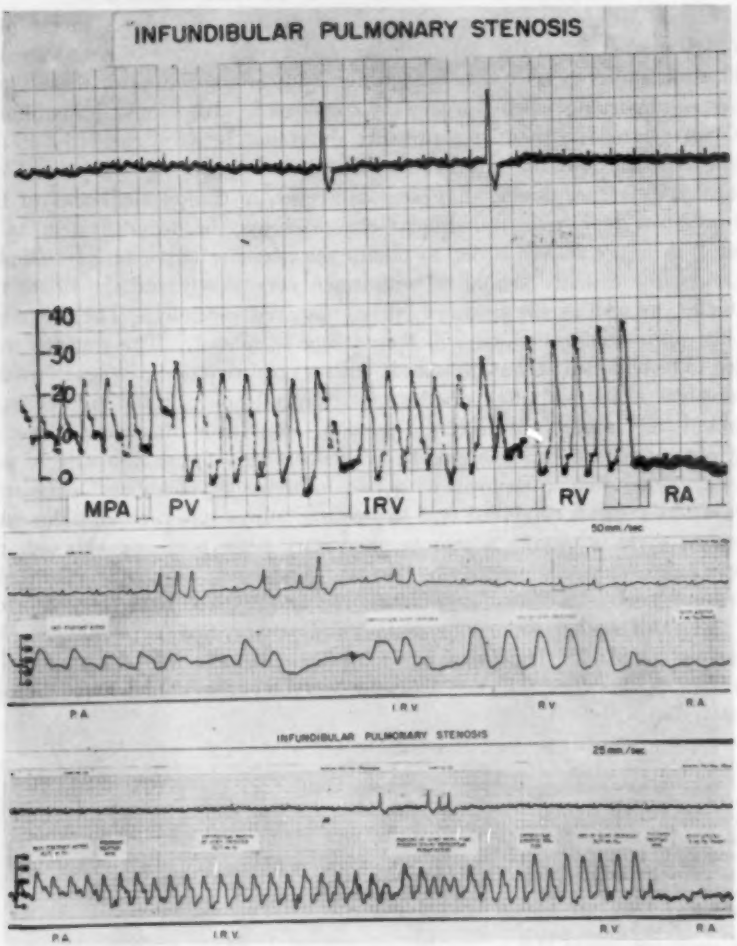
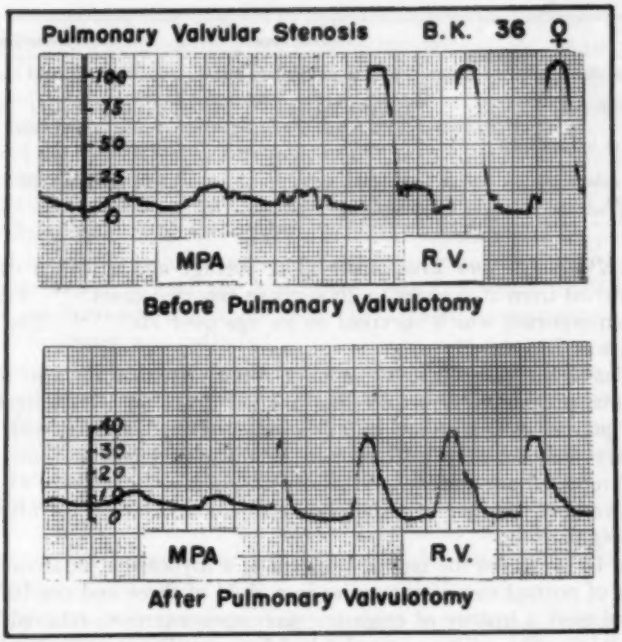


FIG. 4. *Case 1.* The upper tracing shows a case of asymptomatic infundibular stenosis. The lower tracing demonstrates the same case with increased electromanometer speed. The middle tracing shows a poor demonstration of the pressure differences between the pulmonary artery and right ventricle due to rapid withdrawal of the catheter.



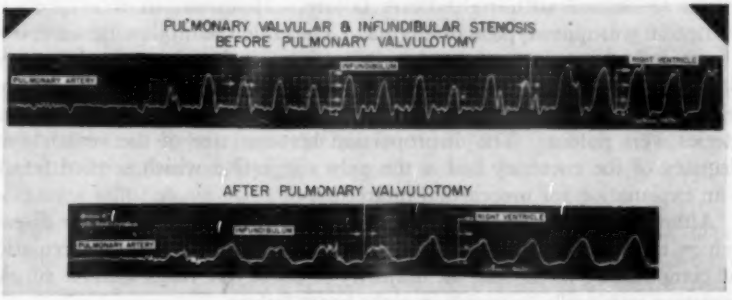


FIG. 5. The upper tracing (*Case 15*) shows the pressure change before and after Brock's procedure with a good result. The lower tracing (*Case 16*) shows the pressure changes before and after pulmonary valvotomy in a combined type of pulmonary stenosis.

On the operating table, the following methods can be used to detect the type of pulmonary stenosis present:

	Valvular Type	Infundibular Type
Location of thrill	Close to pulmonary valve	Within the right ventricular cavity
Sinus of Valsalva	Usually absent	Usually present except in high infundibular type
Visibility of infundibular chamber	Absent	Present
Cardiac catheterization during operation	Valvular type	Infundibular type

VII. *Prognosis and Treatment.* The average age at which death occurred varied from 20.6 years to 26 years in reported cases.[9, 12] Five cases have been reported which survived to an age over 70.[8, 13, 14] The longest survival was 78 years.[14]

We have one case (case 3) of mild pulmonary stenosis who tolerated one normal pregnancy very well, and another (case 9) who tolerated two normal pregnancies without complications. Even patients with severe pulmonary stenosis may tolerate two or three pregnancies quite well.[8, 9] Brock [15] reported one patient with a normal spontaneous delivery 11 months after valvotomy, another who underwent valvotomy during the fifth month of her pregnancy.

Case 12 presented the unique problem of a myocardial infarction in the presence of normal coronary arteries in a child of three and one-half years. The child gave a history of epigastric pain upon exertion, relieved by rest, for several months. These episodes had been attributed to acute liver congestion associated with right heart failure. However, in retrospect, the description was quite typical of angina. The child died following an episode of sustained severe chest pain and an infarction was found, confined primarily to the right ventricle and septum. The pulmonary valve was severely stenotic, the right ventricle markedly hypertrophied, and the coronary arteries were patent. The disproportion between size of the ventricle and adequacy of the coronary bed is the only suggestion which seemed feasible as an explanation for myocardial infarction.

Although several factors may influence the prognosis of this disease, such as the severity of the stenosis, the compensating collateral circulation, and complicating infections, the majority of the severe cases without surgical correction eventually succumb in right heart failure.

Summary

The diagnosis of pulmonary stenosis should be suspected in patients with a harsh systolic murmur, maximal along the second, third or even (infrequently) fourth interspace, with a pulmonary second sound which may vary

from normal to reduplicated or diminished, and with an electrocardiogram which may vary from normal to one indicating right ventricular hypertrophy. The x-ray may be normal or may show a prominent main pulmonary segment with quiet lung shadows. The diagnosis can be proved only by cardiac catheterization. Angiocardiography is unsatisfactory for accurate diagnosis. The diagnosis can usually be made after auscultation, electrocardiography and fluoroscopy. However, this appears to be one disease whose precise presence can be proved only by right heart catheterization. The opinion of the pathologist is unreliable in the recognition of mild obstruction in the atonic dead heart.

Minimal requirement for making the diagnosis should be the presence of a harsh, grade II or greater systolic murmur maximal near the pulmonary area and a difference in pressure gradient from pulmonary artery to right ventricle of 10 mm. of mercury or greater. Any case which just filled these minimal requirements would obviously be a mild, asymptomatic case in which no treatment was indicated.

Cardiac catheterization is the only reliable method for determining the presence of pulmonary stenosis in the intact patient. Pulmonary stenosis is difficult—in fact, impossible—to recognize consistently by angiocardiogram. In the atonic, nondynamic heart, as seen at autopsy, the recognition of mild degrees of pulmonary stenosis may be difficult.

As the surgical technic for pulmonary valvotomy improves and mortality decreases, the indication for surgery will probably become more liberal. However, at the present time surgery should be based on the following indications:

1. Any clinical symptoms to suggest right heart failure, including episodes of syncope, systolic jugular pulse, systolic pulsations of the liver, etc.
2. A decreasing arterial oxygen saturation, probably indicating that the pressure in the right auricle is mounting and blood is shunting across the foramen ovale from right to left.
3. Change in electrocardiographic pattern with widening of the QRS and increasing amplitude and width of the P waves.
4. An initial right ventricular pressure of 70 or greater. This figure is arbitrarily chosen, and as the surgical technic becomes more adept the indications will become more liberal.

The most reliable method of evaluating the success or failure of the operation is to catheterize the right heart prior to and after the valvotomy through the wound in the right ventricle. The surgical approach to the valve with the usual method is blind. The surgeon cannot be certain if he has cut the valve, simply stretched it, or even left it intact. Pressure readings are therefore an important adjunct to the operative technic.

The surgical correction of infundibular stenosis seems blind and crude. In most hands the operative mortality is high; for the present, surgery seems adequate for valvular stenosis but far from ideal for infundibular stenosis.

It is important to realize that although the pressure in the right ventricle may not return to normal after surgery, still the patient may be markedly benefited.

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RUPTURE OF THE INTERVENTRICULAR SEPTUM DUE TO MYOCARDIAL INFARCTION: REPORT OF TWO CASES *

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SEPTAL myocardial infarction has been described in the literature at great length, together with injection studies of the coronary arteries in the infarcted areas, and electrocardiographic correlation. An excellent review by Bond et al.[9] presented a total of 93 cases of septal myocardial infarction with rupture of the interventricular septum. It is amazing that this entity has seldom found its way into textbooks of medicine, cardiology or electrocardiography.

Wilson and Barker [1, 2, 3, 4] extensively investigated bundle branch block. By ligating the bundle branch in dogs they established electrocardiographic patterns of bundle branch block.[5] Following this, it was assumed that the majority of cases of bundle branch block were the result of myocardial infarction involving the anatomic location of the bundle of His and its branches, in the posterior upper part of the interventricular septum. This part is supplied by the right coronary artery, and as this artery is rarely occluded, and is responsible for a small per cent of all myocardial infarctions, this theory is no longer tenable. If we give bundle branch block an electrocardiographic definition of prolongation of the QRS to 0.12 second or longer, then "bundle branch block" could be due either to (1) actual blocking of the bundle branch, or (2) arborization or peri-infarction block, or (3) the prolongation sometimes seen in acute left ventricular failure, or (4) the prolongation sometimes seen in acute right ventricular strain due to pulmonary embolism, or (5) blocking of the Purkinje system. Any of these conditions might be associated with infarction of the septum. Prolongation of the QRS interval was seen in 30 of 80 cases of Myers et al.,[8] but this was probably independent of the size of the infarction, and in the majority of the 30, was independent of the septal infarction altogether. Septal infarction is usually spotty, and can involve the upper, lower or middle parts. Multiple septal infarcts are common. Septal infarction is associated with anterior infarction in 72 per cent of the cases, with posterior infarction in 24 per cent, and occurs as an isolated finding in only 4 per cent.[8]

Symptoms of septal infarction are not characteristically different from those of infarction of other parts of the myocardium, and electrocardiographic diagnosis is important. Electrocardiographic patterns associated with septal infarctions are: (1) auriculoventricular block; (2) right ventricular conduction defects; (3) left ventricular conduction defects; (4) Q waves and/or RS-T segment displacement in right ventricular leads

* Received for publication September 4, 1953.

directly referable to, or at least suggestive of, septal infarction, and (5) absence of direct evidence of septal lesion.

Auriculoventricular block has been noted in only about 4 per cent of cases,[5] and has been variously associated with sinus tachycardia, auricular fibrillation, transient A-V nodal tachycardia, auricular flutter and normal sinus rhythm.

Right ventricular conduction defects have been seen in about 20 per cent of the cases.[6] They comprise prolongation of the QRS interval to 0.12 second or longer, late secondary R waves occurring 0.08 second or more after the beginning of the QRS, and a distinct Q wave replacing or nullifying the early R seen in uncomplicated right bundle branch block.[1, 2, 3, 4] All of these changes are seen in the leads coming from the right precordium, i.e., the right ventricular leads. These abnormal Q waves, associated with elevation of the RS-T segment in leads to the left of the normal transition, would indicate extension of the infarct into the anterolateral portion of the left ventricle. The early R ordinarily seen in right bundle branch block is due to septal activation; and absence of this early R, or decrease in its expected size, or replacement of it by a Q, will depend on the relative sizes of the infarcted and noninfarcted parts of the septum. Large septal infarcts will allow the negative cavity potential of the left ventricle to be transmitted to the right ventricle.

Left ventricular conduction defects, consisting of prolongation of the QRS interval to 0.12 second or longer, and abnormal Q wave and late R in the left ventricular leads, are seen in only about 10 per cent of cases. Activation of the right ventricular musculature is responsible for the negative cavity potential in the right ventricle. This negative cavity potential must be transmitted through the infarcted area in order to produce the early Q wave, or decrease in expected size of the early R. Because the right ventricular musculature is thinner, a larger infarcted area would be required to produce these changes in the leads from the left ventricle.

In the absence of bundle branch block, Q waves and/or displacement of the RS-T segments in leads from the right precordium are signs of septal infarction. Triphasic QRS complexes characterized by a small Q, small R and deep S wave may be seen in V_1 and/or V_2. This form of QRS is sometimes noted in uncomplicated left bundle branch block, and in infarction of the anterior wall of the left ventricle if the transition is far enough to the right, without assuming any septal infarction. Monophasic QS complexes in V_1 and V_2 have been noted in septal infarction, but this is more likely to represent extension to the right ventricle of a large anterior infarction. The contour of the P waves in these leads (V_1 and V_2) may be of help; a steep downstroke of the P wave indicates that the electrode is over the atrium, and that the QRS changes are referable to infarction in the septum, rather than to infarction of the free ventricular wall. Monophasic QS complex in V_2 only, associated with RS complex in V_1, or in leads farther to the

right, such as V_3R, would be unequivocal evidence of septal infarction, especially if the P wave changes mentioned above were present in V_1 and V_2.

Direct evidence of septal infarction is sometimes absent. One may see incomplete patterns fulfilling part, but not all, of the criteria in one of the foregoing categories, or classic displacement of the RS-T segment in V_1 and V_2 without QRS abnormalities in these leads, but accompanied by abnormal Q waves in leads farther to the left.

Perforation

Rupture or perforation of the interventricular septum as a result of septal infarction presents a very characteristic picture. In a patient known to have a septal infarct with findings as presented above, the sudden appearance of a very loud systolic murmur accompanied by rapid deterioration in the patient's condition is classical evidence. The accident usually occurs about four to 12 days following the infarction, being most common from the seventh to the tenth days. The patient suddenly becomes much worse, with renewal or aggravation of the anginal pain, shortness of breath, dyspnea at rest, cyanosis, congestive heart failure, or peripheral vascular collapse.

The murmur has been noted in over 95 per cent of the cases reported, and is absent only with a very large defect. The murmur is loud and rasping, and is accompanied by a palpable thrill in most cases. It is heard best just to the left of the sternum in the fourth intercostal space, but is also heard over the entire precordium. Diastolic murmurs are not characteristic of this condition and, if heard, are probably due to cardiac dilatation.

Most perforations are located in the muscular portion of the septum, near the apex of the heart, but they may occur at any point. Many are multiple; most are small. Hypertension seems to be a definite contributing factor; increased pressure difference between left and right ventricle would increase the possibility of perforation. Taking into account that myocardial infarction in general is more common in men than in women, there is a statistical preponderance of septal infarction with perforation in women as compared with men. The incidence in older age groups is proportionately higher than that of infarction in general. There may be some correlation between long-standing hypertension, longevity and the higher incidence in women. Life expectancy of women is greater than that of men; women rarely have angina and infarction unless they are hypertensive; hypertension is required to produce the pressure gradient necessary for the perforation. Both of my patients were women, one 80 years of age, the other 82, and both had had hypertension for many years.

The prognosis is uniformly bad. Only one patient in 90 lived over five years, and only five patients lived over eight weeks.[9]

Treatment is that outlined for myocardial infarction in general, and comprises rest, oxygen, stimulants, anticoagulants, and supportive and

roborant measures, but is usually futile. Surgical repair of the septal defect, as now practiced in congenital heart disease, might be suggested.

Differential diagnosis would not be difficult if the condition were kept in mind. In any patient with septal infarction, the sudden appearance of a loud systolic sound should be clinically diagnostic. Other causes of systolic sounds occurring in the course of myocardial infarction are: (1) pericarditis with friction rub; (2) rupture of a papillary muscle (which is quite rare), and (3) acute dilatation of the heart. In acute dilatation of the heart the murmur is much softer and much slower to appear. There are some conditions not associated with infarction which might give a similar murmur, but not of so sudden an appearance. Rarely, in subacute bacterial endocarditis, the involved septum ruptures, giving rise to a sudden systolic murmur not previously present.

Case Reports

Case 1. Two or three years prior to admission this 82 year old woman had had an attack of "indigestion" which was not severe, did not require the services of a physician, and was characterized by shortness of breath and pressing substernal pain, and an apprehensive feeling that she was "afraid to breathe." She recovered from this and was ostensibly well until the day prior to admission. After walking to the store, which was unusually severe exercise for her, she developed acute shortness of breath. The day of admission she had a heaviness in her chest, with radiation into the arm. The evening of the day of admission she developed extreme shortness of breath and orthopnea, then became sweaty and apprehensive. She had had no edema and no particular palpitation.

Physical examination on admission to the hospital revealed an overweight, acutely ill, sweaty, cyanotic orthopneic white woman. The oral temperature was 98° F. The blood pressure was 120 mm. of Hg systolic and 70 mm. diastolic in each arm in the reclining position. The pulse was 100, and because of multiple premature contractions was grossly irregular. There was no pulse deficit. There was venous congestion to the level of the angle of the jaw bilaterally. The ocular fundi showed arteriosclerotic retinopathy, grade II, Keith-Wagner classification. There were sibilant and crepitant râles throughout the entire chest anteriorly to the level of the clavicle and posteriorly to the apex. The left border of cardiac dullness was 10 cm. from the midsternal line in the fifth intercostal space. There were no significant murmurs on admission, and no edema was present. The remainder of the physical examination revealed no significant abnormalities.

The red blood count was 3,340,000/cu. mm.; the hemoglobin was 11 gm. or 73 per cent. The white blood count was 16,750/cu. mm., with 82 per cent neutrophils, 16 per cent lymphocytes and 2 per cent monocytes. The Kline serologic test for syphilis was negative. Urinalysis of a voided specimen showed a specific gravity of 1.025, a trace of albumin, no glucose, a few red blood cells, and 30 white blood cells per high power field. Admission electrocardiogram with 12 leads showed the heart rate to be 88; the PR interval was 0.20 second; the QRS was 0.08 second; the QT interval was 0.36 second. The mean electrical axis was plus 60°; there was no axis deviation. There was a 2 mm. Q wave in Lead II, and 3 mm. Q in Leads III and AVF, with slight sagging of the ST segment in these leads. The R wave was absent in Leads V_1, V_2, V_3, V_4 and V_6. There was slight elevation of the RST junction in V_3, and pronounced elevation in V_4. There was a late R wave in V_5. T waves in all the precordial leads were upright. The electrocardiogram was interpreted as

showing an old posterior infarction and a recent anteroseptal infarction. Multiple auricular premature contractions were noted. It was concluded that the patient had had a recent anteroseptal infarction, and had acute pulmonary edema secondary to left ventricular failure.

She was digitalized and started on Dicumarol, and given oxygen and other supportive measures. On the day following admission her chest was much clearer, and her color was good with oxygen. She had no more pain, and was taking fluids by mouth. She was able to lie flat and was putting out urine. The evening of the second day she developed a gallop rhythm at the apex and a temperature of 101° F., but she was still comfortable. On the third day she presented a very loud pericardial friction rub and was having more pain in the chest but no sign of heart failure. On the fourth hospital day she was thought to be doing well. The blood pressure had stabilized at 120 mm. of Hg systolic and 70 mm. diastolic. The temperature was coming down, and she was taking fluids by mouth. She no longer had pain, the chest was resonant throughout, and no râles were heard. Cheyne-Stokes respiration was very pronounced at times but her color was good. About 3:00 p.m. on this fourth day she suddenly went into shock, irregular Cheyne-Stokes respiration became more marked, and the blood pressure was unobtainable. She was given Desoxyn, 10 mg. intramuscularly. Another electrocardiogram, obtained at this time, showed the old posterior infarction, a sinus tachycardia and recent anteroseptal infarction. The intervals were unchanged. Lead V_1 presented a 2 mm. Q wave, a late secondary R (0.08 second following onset of QRS), and inverted T. There were a 7 mm. Q and marked elevation of the RST segment, and late inversion of the T waves in Leads V_2, V_3 and V_4. Lead V_5 showed a 4 mm. Q, late secondary R and upright T. Lead V_6 showed a small initial Q, a 5 mm. R and upright T. Xiphoid lead showed a QR type of complex.

About three hours after this second electrocardiogram was taken the patient was found to have a very loud, rasping, blowing systolic precordial murmur which definitely had not been present before. These findings were interpreted to indicate septal perforation. At 9:05 p.m. respiration ceased.

At autopsy, the body was that of a well developed, obese woman without gross deformities or abnormalities. The heart weighed 500 gm. A fairly well circumscribed area, involving the apex and about two thirds of the anterior portion of the myocardium, was soft and roughened. The left ventricle was larger than normal, and the anterior portion of the left ventricular wall was thin over an area of about 10 to 15 cm., extending to the apex. The thinnest part was at the extreme apex. Other areas about 25 to 30 mm. in thickness were beefy red and bright. The distal third of the septum was extremely thin and soft, and in one area there was a small, slitlike perforation. Both surfaces of the septum were roughened. The aorta showed atherosclerosis. The lumen of the left coronary artery appeared to be of normal size for about 3 cm., then abruptly became narrowed and filled solidly with a thrombus about 25 mm. long. The vessel wall was hard, and cut with resistance throughout the entire course.

The left kidney weighed 225 gm. The capsule was adherent; the surfaces were coarsely granular and red. The cortex and medulla were thin. The pelvis and calyces were dilated; the peripelvic fat was increased. The right kidney weighed 200 gm., and was in every way similar. No other significant abnormalities were noted on the gross examination. Microscopic examination was not particularly helpful in the diagnosis of this case. There was advanced necrosis of cardiac muscle with an intense infiltration of leukocytes, representing recent myocardial infarction.

The gross anatomic diagnoses were: (1) generalized arteriosclerosis; (2) thrombosis of the left coronary artery, 3 cm. from the orifice; (3) myocardial infarction involving the free left ventricular wall and the interventricular septum; (4)

antemortem septal perforation; (5) pericarditis; (6) passive congestion of the lungs, liver, spleen and kidneys, and (7) chronic nephritis with hydronephrosis.

Case 2. This 80 year old woman had been a known hypertensive for many years, perhaps as many as 25. The systolic pressure had fluctuated between 230 mm. and 160 mm., and the diastolic between 110 mm. and 90 mm. During this period she had had some episodes of abdominal cramping, associated with sweating and diarrhea. There had been no vomiting, hematemesis, jaundice or weight loss. No x-rays, electrocardiograms or other studies had been made. About five months prior to admission she had had a cerebral vascular accident with transient aphasia and right hemiparesis, but this cleared without residual. About 5:00 a.m. on the day of admission she suddenly developed a severe crushing pain in the chest, radiating down both arms to the wrists, and associated with nausea, vomiting, sweating and dyspnea. She was seen in the home, and given morphine and caffeine sodium benzoate. Her condition improved sufficiently to allow her to be brought to the hospital by ambulance. There was no history of orthopnea, exertional dyspnea or particular palpitation prior to this acute episode.

Physical examination on admission to the hospital revealed a well preserved, small boned, pleasant appearing little woman, obviously desperately ill. The skin was gray, cold and clammy. She was slightly dyspneic and orthopneic. The rectal temperature was 102° F. The pulse was 70 and regular, and the blood pressure was 160 mm. of Hg systolic and 130 mm. diastolic in the right arm reclining. She was edentulous. The pupils were round, regular and equal, but constricted by morphine. The precordium was overactive, and the apex impulse forceful. The point of maximal intensity of the apex beat was 8 cm. from the midsternal line in the fifth intercostal space. The left border of cardiac dullness was 9 cm. from the midsternal line in the fifth intercostal space. The rhythm was regular. There was a very faint grade I systolic murmur heard at the apex which was not transmitted. The lung fields were resonant throughout, and the breath and voice sounds were normal. No râles were heard. The remainder of the physical examination revealed no significant abnormalities. There was no sign of congestive failure.

The red blood count was 4,500,000/cu. mm.; the hemoglobin was 14.5 gm. per cent or 94 per cent. The white blood cell count was 12,750/cu. mm., with 83 per cent filamented neutrophils, 9 per cent nonfilamented neutrophils, 6 lymphocytes and 2 monocytes. The Eagle serologic test for syphilis was negative. The prothrombin time was 24 seconds, compared with a control of 15 seconds. The entire 12 lead electrocardiogram is reproduced in figure 1. The auricular and ventricular rates were 84, sinus mechanism. The PR interval was 0.16 second, QRS interval was 0.16 second in Leads II and III. The QT interval was 0.44 second. The mean electrical axis was plus 30 degrees. There was no axis deviation. There were deep broad S waves in Leads I and II. Leads III and AVF showed W shaped S′ following a 5 mm. deep S wave. A mirror of this effect was noted in AVR. There were 10 mm. Q waves, followed by late R waves (0.12 second after beginning of Q), in Leads V_1, V_2 and V_3. There was pronounced elevation of the ST segment in Leads V_2, V_3 and V_4, and sagging of the ST segment in Lead V_6. Lead V_4 showed a QRSR′ type of ventricular complex. The electrocardiogram was interpreted as showing right bundle branch block, and acute anteroseptal infarction with injury effect. It was concluded from this history and these findings that the patient had had a recent anteroseptal myocardial infarction.

She was started on oxygen, morphine, and caffeine sodium benzoate, and Dicumarol. She continued to have chest pain radiating into both arms, and paresthesias of the hands. She had several episodes of vomiting of blood-tinged material. About 5:30 p.m. of the day of admission (some 12 hours after the onset of her chest pain) she suddenly became worse, the blood pressure was unobtainable, the apical pulse rate

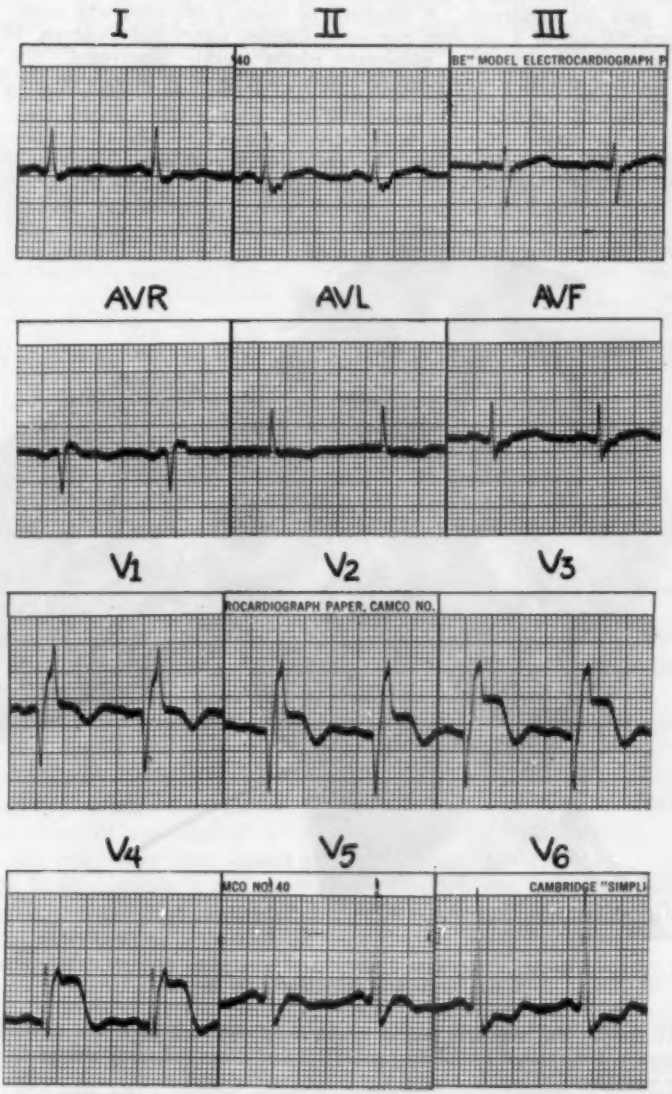


FIG. 1. Twelve lead electrocardiogram from case 2, showing anteroseptal myocardial infarction. For complete explanation of the electrocardiographic findings, see text.

quickened to about 120 per minute, and a very harsh, very loud grade IV systolic murmur made its appearance. A diagnosis of septal perforation was made. She was given 500 c.c. of 5 per cent glucose in distilled water, and Desoxyn, 10 mg. intramuscularly. Severe acute pulmonary edema quickly supervened. She was anuric, and died at 1:10 p.m., the second hospital day, about 20 hours after the septal perforation.

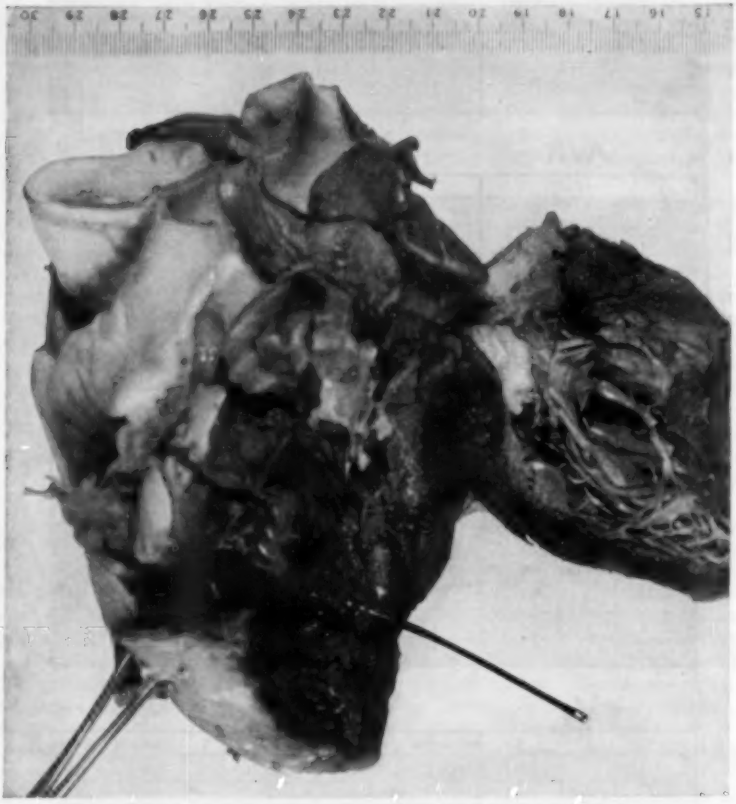


FIG. 2. Autopsy specimen from case 2, with silver wire probe through slitlike perforation in the interventricular septum near the apex.

At autopsy, the body was that of a well developed, well preserved white woman who appeared the stated age of 80 years. Neither gross deformity nor gross abnormality was noted.

The heart was normal in size. The visceral and parietal pericardium was smooth and glistening. There was a moderate amount of epicardial fat. On the anterior wall, in the region of the lower half of the septum, there was a very soft area, and this had undergone grayish discoloration. No emboli were noted in the branches of the

pulmonary arteries. In the center of the lower third of the septum there was a thin, soft area, and a recent hemorrhage within the musculature. When the left ventricle was opened a perforation in the septum became visible. This was rather small (figure 2), but apparently sufficient to allow blood to flow from the left ventricle to the right. There was a small, apparently very recent thrombus in the left coronary artery about 2 cm. below its origin. On cut section there was reddish discoloration suggestive of recent myocardial infarction, involving the lower third of the septum and the free walls of the left and right ventricles immediately adjoining the septum. The atria were grossly normal, and the valves were intact. The aorta showed atherosclerosis, as did the coronary arteries. The liver showed some nutmeg mottling. The lungs exuded pink fluid when cut, and the dependent portions had lost most of the normal crepitation. No other significant abnormalities were noted on the gross examination. Microscopic examinations were not particularly helpful in the diagnosis.

The gross anatomic diagnoses were: (1) generalized atherosclerosis; (2) coronary thrombosis; (3) myocardial infarction involving the free anterior surfaces of the left and right ventricles, and the lower third of the interventricular septum; (4) perforation of the interventricular septum, due to infarction, and (5) passive congestion of the lungs and liver.

Comment

1. Septal myocardial infarction with rupture of the interventricular septum due to myocardial infarction is discussed from the standpoint of electrocardiography and clinical observations. Reference is made to an excellent review by Bond et al.,[9] in 1953 and to the classic article by Myers et al.[8] in 1949.

2. Two cases of septal perforation due to septal infarction are presented. Both were diagnosed antemortem, both were rapidly fatal, and the diagnoses were confirmed by autopsy. In one case, photographs of the 12 lead electrocardiogram and photographs of the autopsy specimen are shown.

3. Although this condition has been discussed at length in the literature, and much study has been given to it, it has not found its way into the textbooks of medicine, cardiology or electrocardiography.

4. Diagnosis seems to be fairly obvious in most of the cases, and depends upon the sudden appearance of a loud systolic murmur not previously heard, and a precipitous change in the patient's general condition. A patient with known septal infarction suddenly becomes much worse, with renewal or aggravation of the anginal pain, shortness of breath, dyspnea at rest, cyanosis, congestive heart failure and peripheral vascular collapse.

5. The prognosis is uniformly bad, and treatment is futile. It is suggested that a surgical closure of the perforation such as that used in congenital heart disease be considered.

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CURRENT TREATMENT OF TUBERCULOUS MENINGITIS: A PRELIMINARY REPORT*

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The authors are reporting 16 consecutive cases of tuberculous meningitis started on treatment between June, 1952, and March, 1953. Five of the 16 patients also had miliary tuberculosis. All of these patients received streptomycin plus sodium para-aminosalicylic acid (sodium PAS) plus isoniazid.

The purpose of this report is to suggest that patients with tuberculous meningitis respond quite favorably to current methods of treatment. A comparison of the survival rates among 63 patients with tuberculous meningitis, with and without miliary tuberculosis, treated on three different regimens, reveals substantial improvement during the past few years (table 1). Eight months after treatment was started 15.6 per cent survived with

Table I

Survival Rates of Tuberculous Meningitis Eight Months after Starting Treatment

Regimens*	Number of Patients		
	Meningitis	Mil. Meningitis	Living
Streptomycin for 120 days	22	10	5 (15.6%)
SM + NaPAS for 1 Yr.+	10	5	9 (60.0%)
SM + NaPAS + INH for 1 Yr.+	11	5	14 (87.5%)
	43	20	28 (44.4%)

* Dosages: SM 2.0 g.d.; NaPAS 16.0 g.d.; INH 800–300 mg. d.

short-term (120 days) streptomycin therapy; 60 per cent survived on long-term treatment with streptomycin plus sodium PAS; and 87.5 per cent have survived on prolonged treatment with streptomycin plus sodium PAS plus isoniazid.

While our results may seem unduly optimistic, they are not unique with us and are quite comparable to several recent reports.[2, 3, 4, 5, 12, 13, 16]

Current Dosage Regimen

At the start of treatment, patients with tuberculous meningitis received 2 gm. of streptomycin daily, plus at least 16 gm. of sodium PAS daily, and usually 10 mg. of isoniazid per kilogram of body weight daily. The dosage

* Received for publication December 9, 1953. (Presented at the Midwest Regional Meeting of the American College of Physicians, Milwaukee, Wisconsin, November 21, 1953.)
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of isoniazid was reduced to 6 or 7 mg. per kilogram daily after the first few weeks, and to 4 or 5 mg. per kilogram of body weight daily after convalescence was well established. The dosage of streptomycin was often reduced to 1 gm. daily after the first six months of therapy. All three drugs were given parenterally while the patients were in coma and until oral administration of sodium PAS and isoniazid became feasible. The duration of therapy was projected for a minimum of one year and usually longer. One recent report [4] suggested that the frequency of administration and the dosages of all three drugs may be considerably reduced without loss of effectiveness.

Until isoniazid became available the majority of investigators believed in the necessity of administering streptomycin intrathecally. The writers were not convinced of this necessity and, except for one case started elsewhere, have not used this route of administration since 1949. This procedure may be desirable in a case that develops a relapse following initial improvement, but in the authors' experience with 35 cases treated during the past three years no such relapse has occurred.

Clinical Status at the Start of Treatment

Background factors of age, race, temperature, state of consciousness, neurologic findings and the duration of symptoms before starting treatment are recorded in table 2. All 16 patients were male veterans ranging between 26 and 60 years of age. Thirteen of the 16 patients were between 26 and 44 years of age. Thirteen of the 16 patients were Negro and three were white. Considering the usual proportion of Negro to white patients on our service, the incidence of tuberculous meningitis was approximately five times as great in the former race.

All 16 patients had proved tuberculosis of other systems, such as pulmonary tuberculosis, miliary tuberculosis, tuberculous adenitis, and tuberculosis of the genitourinary or osseous systems. The clinical, neurologic and cerebrospinal fluid findings were typical of those found in our proved cases of tuberculous meningitis previously reported.

Before treatment, the temperatures of 11 patients ranged from approximately 103° to 105° F.; four ranged from approximately 101° to 102° F., and one patient's temperature was 99° F.

At the start of treatment six patients were in coma, four in stupor, four were confused or drowsy or both, and two patients were alert. Bladder and bowel incontinence was noted in six cases, paralysis of cranial or peripheral nerves in four, and nuchal rigidity or abnormal reflexes, or both, were present in all but one case. Only one patient was alert and presented no abnormal neurologic findings.

If the state of consciousness and neurologic findings should be given any weight in the evaluation of the stage of disease at the time treatment was

started, the above findings would suggest that treatment was started late in six cases, relatively late in four, relatively early in four, and early in two cases.

The history of duration of symptoms before treatment ranged from three days to three months and failed to correlate well with the state of consciousness and neurologic abnormalities noted at the start of treatment. For example, two patients were incontinent and in coma on admission, yet the families stated these patients were completely well and without complaints up to within three and six days of admission. Again, one of the two patients, completely alert and with only nuchal rigidity and moderately abnor-

TABLE II

Clinical Status of Patients with Tuberculous Meningitis

Case No.	Age	Race	Before Treatment			
			Temp.	Duration of Symptoms Pre-Rx* (days)	State of Consciousness	Neurologic Abnormalities
1	34	N	99	85	++	+
2	31	N	101	3	0	0
3	60	W	102	12	+++	++++
4	27	N	103	10	++	+
5	36	N	102	14	+++	++
6	38	N	103	13	+++	++
7	58	N	104	12	++++	++++
8	26	N	104	?	++++	++++
9	41	W	104	29	++++	++++
10	35	N	104	3	++++	++
11	43	W	103	15	++	+
*12	30	N	103	10	++	++
*13	49	N	105	72	++++	++++
*14	26	N	105	3	++++	++
*15	44	N	103	3	+++	++++
*16	30	N	101	45	0	+

* = Combined miliary-meningeal tuberculosis.

State of Consciousness—0 = alert; + = drowsy, irritable; ++ = confused, irrational; +++ = stupor; ++++ = coma.

Neurologic Status—0 = normal; + = nuchal rigidity; ++ = grossly abnormal reflexes; +++ = paralysis; ++++ = bowel and bladder incontinence.

mal reflexes, insisted that he had had persistent headaches and fever for the preceding six weeks. Experiences such as these have made us cautious in deciding, merely on a history of duration of symptoms, whether treatment was started early or late; and we tend to place greater emphasis on objective findings present on admission, such as the presence of coma, stupor, incontinence and paralysis.

Whereas the evaluation of coma versus stupor may be subject to the inaccuracies of personal interpretation by different physicians, bladder and bowel incontinence were objective phenomena that suggest those patients were not in an early phase of their disease.

Clinical Response to Treatment

One of these 16 patients died 17 hours after admission, another on the eleventh day of treatment, and 14 (87.5 per cent) have survived to date (eight to 18 months). In the 14 survivors, the temperature returned to normal within four weeks in 13 cases; one (case 8) intermittently has a fever associated with recurrent episodes of complicating sepsis. The latter patient was treated with unknown quantities of streptomycin and PAS over a total period of approximately eight months for tuberculous meningitis at two other hospitals. He left both institutions against medical advice. Two months after leaving the second hospital he was admitted to our institution in coma, critically ill with sepsis from multiple severe decubitus ulcers, bladder and bowel incontinence, contractures of both lower extremities and grossly abnormal cerebrospinal fluid (table 3, case 8). Eight months after starting treatment at our hospital he had no signs of active tuberculous meningitis and his cerebrospinal fluid findings were as follows: protein, 49 mg. per cent; cells, 0; sugar, 70 mg. per cent.

Eight of the 14 survivors were admitted in coma or stupor. They were usually sufficiently improved to take oral medication within a week or two. Within six weeks of starting treatment the sensorium had cleared completely in 12 of the 14 survivors, one cleared within four months (case 13), and one (case 8) has severe sequelae. Abnormal neurologic findings cleared within a month of starting treatment in 12 of the 14 survivors, and two (cases 13 and 8) have sequelae.

Sequelae and stigmata of tuberculous meningitis persisted in two of the 14 survivors. One patient (case 13) had a left hemiplegia when he left contrary to medical advice. He had not suffered a clinical relapse and was walking with little difficulty eight months after treatment was started. The other patient (case 8) has severe brain damage and marked contractures of both lower extremities, and may die because of sepsis from severe decubiti and recurrent genitourinary infections if not from tuberculous meningitis.

Serial roentgenograms revealed marked to complete clearing of the miliary lesions within two to four months in the five cases with associated miliary tuberculosis. The roentgenograms of one patient (case 4) clearly demonstrated two large distinct shadows typical of Pott's abscesses. At the end of four months of treatment for tuberculous meningitis both shadows had completely disappeared.

The Effect of Treatment on Cerebrospinal Fluid Findings

Four significant cerebrospinal fluid elements were selected and recorded (table 3). The protein content was elevated (80 to 500 mg. per cent) before treatment in 15 cases. It subsided to less than 75 mg. per cent in 12 of the 14 survivors by the eighth month, and was 53 mg. per cent or less at the fourth month of treatment in six patients. Protein content appeared to be the last of the four elements to return to normal, and, in

TABLE III

Cerebrospinal Fluid Findings (C.S.F.)* in Patients Treated for Tuberculous Meningitis

Case No.	C.S.F.	Pre-Rx	1 Mo.	2 Mo.	4 Mo.	8 Mo.
1	P.	160	396	330	187	103
	C.	150		270	72	2
	S.	58	47	48	70	79
	Cl.	660	635	680	—	768
2	P.	120	—	—	53	†
	C.	68	—	—	2	
	S.	46	—	—	70	
	Cl.	—	—	—	—	
3	P.	180	—	—	53	72
	C.	80	—	—	2	0
	S.	22.5	—	—	85	75
	Cl.	—	—	—	—	705
4	P.	98	—	128	63	36
	C.	202	—	28	4	0
	S.	47	—	58	70	70
	Cl.	—	—	779	—	—
5	P.	280	136	148	40	37
	C.	240	0	6	10	2
	S.	38	40	43	65	70
	Cl.	—	—	—	682	673
6	P.	210	110	74	60	52
	C.	45	49	10	12	0
	S.	22	—	70	—	—
	Cl.	622	654	—	700	—
7	P.	395	Death 17 hrs. after adm.			
	C.	26				
	S.	24				
	Cl.	—				
8	P.	500	500	226	158	49
	C.	74	106	0	18	0
	S.	84	97	—	46	70
	Cl.	—	592	—	682	—
9	P.	260	Death on 11th day of Rx			
	C.	540				
	S.	27				
	Cl.	—				
10	P.	320	147	—	78	27
	C.	124	36	—	0	0
	S.	21	—	—	80	75
	Cl.	648	605	—	679	675
11	P.	80	31	—	—	26
	C.	78	2	—	—	4
	S.	39	70	—	—	80
	Cl.	—	—	—	—	682
12	P.	140	128	87.5	50	44
	C.	25	17	8	12	0
	S.	71	70	70	—	75
	Cl.	645	—	—	—	—
13	P.	125	100	100	52	C.M.A.
	C.	—	123	19	5	
	S.	53	27	58	62	
	Cl.	—	660	680	—	
14	P.	240	160	64	91	97
	C.	16	42	8	82	2
	S.	32	40	47	56	50
	Cl.	693	680	732	—	—
15	P.	31	50	†		
	C.	10	0			
	S.	85	80			
	Cl.	—	—			
16	P.	94	—	70	32	25
	C.	54	—	0	0	0
	S.	30	—	56	85	80
	Cl.	—	—	—	—	683

Tubercle bacilli were recovered from the cerebrospinal fluid of cases 2, 3, 8, 12, 13 and 15.

* P = protein; C = cells; S = sugar; Cl. = Chlorides; Pre-Rx = before treatment; C.M.A. = left hospital contrary to medical advice.

† Refused further lumbar punctures.

our previous series, occasionally failed to return to normal levels in less than a year and a half.

The total cell count before treatment ranged from 10 to 540. It returned to essentially normal limits in all 14 survivors by the eighth month, and reached normal levels within four months in the majority of cases.

The sugar content, before treatment, was found to be more than 45 mg. per cent in seven cases, 30 to 39 mg. per cent in four, and less than 30 mg. per cent in five cases. It rose to more than 60 mg. per cent in most of the survivors within four months, and in all but one (case 14) by the end of eight months of therapy.

The chloride content of the cerebrospinal fluid correlated reasonably well with the sugar content in those cases where both were determined simultaneously.

In our earlier series [6, 7] the streptomycin levels of the cerebrospinal fluid were of aid in the early diagnosis of complicating tuberculous meningitis in those cases receiving treatment for miliary tuberculosis, and were also helpful in following the response to treatment. Though nonspecific, the Levinson test has been useful in supporting the probable diagnosis of tuberculous meningitis.

Since we have abandoned intrathecal therapy, we frequently have only one or two lumbar punctures during the first month of therapy when bacilli are most likely to be recovered. Meanwhile the mortality rate has sharply declined, so that few patients come to postmortem examinations. Consequently, bacteriologic and particularly postmortem confirmation of the clinical diagnosis has been substantially curtailed in our more recent cases.

The diagnosis of tuberculous meningitis was proved bacteriologically in only six of the 16 patients ante mortem, and all six survived. Tubercle bacilli were recovered from the cerebrospinal fluid of five of the seven patients whose initial spinal fluid sugar content was in excess of 45 mg. per cent, and in only one of the nine whose sugar concentration was less than 40 mg. per cent. Of the two unproved cases whose initial sugar content was in excess of 45 mg. per cent, definite abnormalities of the cerebrospinal fluid persisted for more than four months in one (case 1) and more than two months in the other (case 4). Thus the cerebrospinal fluid findings suggested a chronic rather than an acute involvement of the central nervous system in the latter two cases.

Toxicity

One patient (case 15) inadvertently received 15 mg. of isoniazid per kilogram of body weight and developed status epilepticus on the fifth day of therapy. Isoniazid therapy was omitted for one day and then the dosage was reduced to 8 mg. per kilogram per day, following which he made an uneventful recovery. His cerebrospinal fluid was completely normal at one month. After one month of treatment the dosage of isoniazid was reduced to 5 mg. per kilogram daily, yet he developed a toxic psychosis in the seventh month of therapy which cleared five days after isoniazid was stopped. He has been continued on therapy with streptomycin plus PAS to date.

Another patient developed a paranoid psychosis while receiving 4 mg. of isoniazid per kilogram of body weight daily. Isoniazid therapy was omitted for two weeks but his psychosis did not improve. Two psychiatrists were of the opinion that isoniazid was not the cause of the psychosis. Isoniazid therapy was resumed and the psychosis later cleared, only to recur two months later. In spite of our abandoning isoniazid therapy two months ago, his psychosis has not improved. No other serious toxic manifestations were encountered in any of the remaining cases.

Discussion

Tuberculous meningitis was uniformly fatal prior to the advent of streptomycin therapy. Whereas short courses of streptomycin apparently saved an occasional patient, adding PAS and prolonging the original course of therapy markedly improved the percentage of survivors (figure 1). The addition of isoniazid holds promise of further improving the survival rate (87.5 per cent at eight months). Although one may expect further losses with longer observation periods, we have reason to hope for a recovery rate of 75 per cent or more with the use of drugs currently available. Obviously some will survive only to die later of causes other than tuberculous meningitis per se. Current follow-up information was obtained in all but

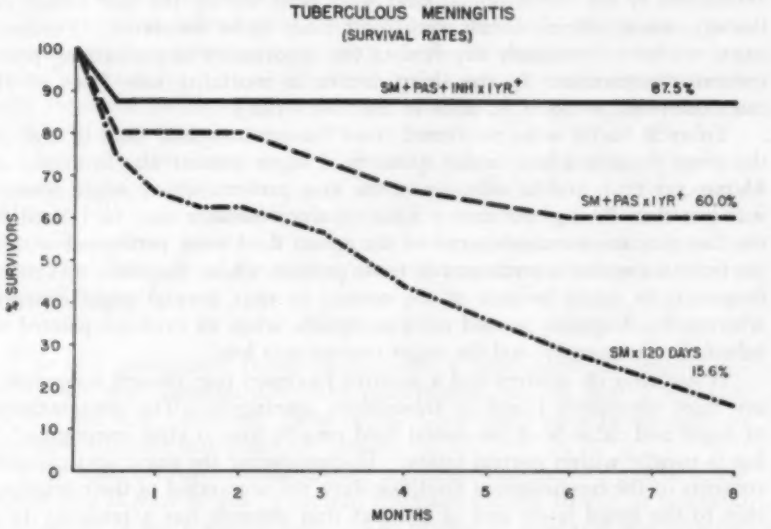


Fig. 1.

two of the 28 survivors of all three regimens (table 1). The two patients lost to study were known to be clinically well one year ago. One patient of the first series died 11 months after starting treatment on streptomycin alone in 1947. Perhaps fortuitously, of the patients followed during the past five years, no patient who survived eight months after beginning treatment has died.

The presence of associated miliary tuberculosis has not affected the survival rates of our patients adversely since initiation of prolonged combined chemotherapy. All five patients with combined miliary-meningeal tuberculosis, in the group herein reported, were living eight to 18 months after beginning treatment.

In our first series of 32 patients, the diagnosis of tuberculous meningitis was supported by recovering tubercle bacilli from the cerebrospinal fluid of 17 patients, solely by postmortem examination in eight; it was not confirmed in seven cases (six dead and one living). In our second series of 15 patients, the diagnosis was supported by recovery of tubercle bacilli in 11 cases, by postmortem examination in two; it was not confirmed in two cases (one dead and one living). During the past seven years postmortem examinations were done in 28 of the 36 fatal cases and in no case was the diagnosis of tuberculous meningitis found to be in error. It must be emphasized that the cerebrospinal fluid was examined almost every other day in the greater part of the first series of 32 patients.

In the current series of 16 cases herein reported, only one or two examinations of the cerebrospinal fluid were done during the first month of therapy, when tubercle bacilli were most likely to be recovered. Furthermore, we were fortunately deprived of the opportunity of performing postmortem examinations by the sharp decline in mortality rate (two of 16 cases compared to 28 of 32 cases in the first series).

Tubercle bacilli were recovered from the cerebrospinal fluid of five of the seven patients whose initial spinal fluid sugar content was in excess of 45 mg. per cent, and in only one of the nine patients whose sugar content was less than 40 mg. per cent. This apparent paradox may be related to the fact that more examinations of the spinal fluid were performed within the first two weeks of treatment in those patients whose diagnosis was more frequently in doubt because of the normal or near normal sugar content, whereas the diagnosis seemed more acceptable when all evidence pointed to tuberculous meningitis and the sugar content was low.

A low chloride content and a positive Levinson test, though nonspecific, are most commonly found in tuberculous meningitis. The concentration of sugar and chloride of the spinal fluid may be low in viral meningitis,[8, 14] but is usually within normal limits. In considering the sugar and chloride contents of the cerebrospinal fluid, we were not unmindful of their relationship to the blood levels and of the fact that chloride has a tendency to a reciprocal relationship to the protein content.

Though the clinical and neurologic findings may be quite similar in many varieties of meningitis, the course, response to treatment and the cerebrospinal fluid findings are usually quite different. Adams[9] states that the three most common causes of chronic meningitis associated with cerebrospinal fluid findings of increased protein, elevated cell count with lymphocytes or mononuclear cells predominating and a low sugar content, are tuberculosis, torulosis and carcinomatosis of the meninges. Carcinomatosis of the meninges is still hopelessly and relentlessly fatal. Torular meningitis is almost always fatal, though an occasional case has apparently recovered.[17]

Adequate examinations of the cerebrospinal fluid for concentration of proteins, sugar and chlorides, differential cytology, presence of parasites,

smears, cultures and animal inoculations will usually reveal the common causes of meningitis or exclude them. Serologic tests such as complement fixation tests, agglutination tests, neutralization tests and skin tests, including the Frei test, are helpful in the differential diagnosis of various viral, syphilitic and leptospiral meningitides, as well as toxoplasmosis, brucellosis and other infections.

The chief diagnostic difficulties encountered by the authors during the past seven years were due to involvement of the central nervous system by viral or fungal infections and by metastatic or primary neoplasms. At necropsy the clinical diagnosis in all fatal cases of tuberculous meningitis was confirmed. Meanwhile no new case of tuberculous meningitis was discovered at necropsy, and no case came to postmortem examination with a mistaken diagnosis of tuberculous meningitis.

With survival rates approaching 90 per cent at eight months, it is proper to scrutinize the evidence upon which the diagnosis of tuberculous meningitis was based. However, if one insists upon the recovery of tubercle bacilli from the cerebrospinal fluid, the survival rate among our patients would be 100 per cent for the past three years.

Admittedly, the diagnosis of tuberculous meningitis can be proved beyond all doubt only by recovery of tubercle bacilli from the cerebrospinal fluid or by histologic examination and recovery of tubercle bacilli at necropsy. Otherwise, as Bunn has stated,[5] the diagnosis depends almost solely upon the honesty and integrity of the person investigating the patient and his cerebrospinal fluid.

Summary

This is a preliminary report of 16 cases of tuberculous meningitis, including five with associated miliary tuberculosis, treated during the past year and one-half. Fourteen patients (87.5 per cent) were living eight to 18 months after the institution of therapy.

At the start of treatment the dosage regimen consisted of 2 gm. of streptomycin plus at least 16 gm. of sodium PAS and usually 10 mg. of isoniazid per kilogram of body weight daily. The dosage of isoniazid was reduced to 6 or 7 mg. per kilogram daily after the first few weeks, and to 4 or 5 mg. per kilogram of body weight daily after convalescence was well established. The dosage of streptomycin was often reduced to 1 gm. daily after the first six months of therapy. The duration of therapy was projected for a minimum of one year and usually longer. All three drugs were given parenterally while the patients were in coma or stupor and until oral administration of sodium PAS and isoniazid became feasible.

Prior to the advent of streptomycin therapy none of our patients with tuberculous meningitis survived. The survival rates at eight months were 15.6 per cent on short-term streptomycin therapy, 60 per cent on prolonged treatment with streptomycin plus sodium PAS, and 87.5 per cent on prolonged therapy with streptomycin plus sodium PAS plus isoniazid.

The current survival rates of patients with tuberculous meningitis are very encouraging provided treatment with a combination of antituberculous drugs is started early and given continuously for a long period of time.

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THE CLINICAL MANIFESTATIONS OF ESSENTIAL POLYANGIITIS (PERIARTERITIS NODOSA), WITH EMPHASIS ON THE HEPATIC MANIFESTATIONS *

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Essential polyangiitis (periarteritis nodosa, polyarteritis nodosa, panarteritis, polyangiitis and necrotizing arteritis) is a primary disease of the vascular system of unknown etiology with protean clinical manifestations.

We became interested in the hepatic manifestations of this disease when two such patients were admitted to Percy Jones Army Hospital within a period of six months. A review of the available literature confirmed the rarity of these cases. It is our purpose to present the clinical manifestations of essential polyangiitis in 200 cases reported in the English literature since 1941, and in 230 cases taken from the autopsy protocols in the files of the Armed Forces Institute of Pathology, with particular reference to the hepatic manifestations clinically.

Historical

Michaelis and Matanni in 1755 are credited by Lamb [45] with the original gross description of the disease. However, most authors credit Rokitansky in 1852 with the original description of the lesions at necropsy. In 1866, Kussmaul and Maier [42] recognized the disease as a clinical syndrome when they reported two cases of a "hereditary undescribed peculiar disease of the arteries which is accompanied by Bright's disease and is a rapidly progressive general paralysis of muscles" which they called periarteritis nodosa. An extensive literature has developed since then as more cases have been recognized and reported. The exact number of reported cases is unknown; however, Boyd [9] in 1938 was able to collect 395. Subsequent to that date, we have collected 200 cases in the available English literature alone.

Excellent reviews have been published by Lamb,[45] Singer,[82] Curtis and Coffey,[16] Middleton and McCarter,[62] Spiegel,[86] Harris, Lynch and O'Hare,[29] Boyd,[9] and Miller and Daley.[64]

Etiology

Essential polyangiitis has been attributed to (1) specific bacterial infections, i.e., streptococci, gonococci, meningococci, tubercle bacilli, and treponema, (2) toxic injury, (3) diseases of the central nervous system,

* Received for publication November 23, 1953.
Material at the Armed Forces Institute of Pathology was made available by the Director, Brig. General E. DeCoursey.

and (4) virus infections. However, none of these has been proved to be the etiologic agent. Gruber [27] first suggested that the disease might be due to hypersensitivity. Clark and Kaplan [13] in 1937 first reported finding the lesions of periarteritis nodosa at autopsy in two patients dying of serum sickness. Rich [72] in 1942 reported seven cases which appeared to be the result of serum sickness. Subsequently, Rich and Gregory [73] were able to reproduce lesions that were indistinguishable from periarteritis nodosa by injecting horse serum into sensitized rabbits. Most workers believe that periarteritis nodosa is a nonspecific hypersensitivity phenomenon. The responsible antigen is usually considered to be bacterial, but hypersensitivity to sulfonamides, desoxycorticosterone acetate, thiourea, organic arsenicals, iodine and penicillin have been suspected as etiologic agents.

The incidence of the disease is unknown. Klotz [40] reported two cases among 3,000 autopsies, and Bernstein [7] six cases among 13,000 autopsies. Griffith [26] reported 16 cases among 19,242 autopsied cases at Los Angeles County Hospital. Rich [72, 74] believes the disease is increasing in incidence. Thirty-eight cases have been observed at the Johns Hopkins Hospital, 84 per cent of these since 1936 (introduction of sulfonamides). There was only one case among 1,902 autopsies during the five year period 1916–1920, whereas there were 17 cases among 1,855 autopsies during the three and a half year period 1941 to July, 1944. The fact that 227 of the 230 cases from the Armed Forces Institute of Pathology occurred since 1939 lends support to Rich's belief.

The disease predominates among males, and has occurred at ages ranging from 10 days to 77 years; however, 43 per cent of the reported cases have occurred between 20 and 40 years of age.

The prognosis was thought to be uniformly fatal within a few months until Arkin [3] introduced the concept of healed periarteritis nodosa. The mortality rate is still extremely high among diagnosed cases; however, there have been several authenticated cases of apparent recovery. The average duration, according to Harris,[29] is 8.6 months. Klein [39] was able to collect seven cases with a duration of two to 15 years before demise.

Pathology

The disease process involves chiefly the small elastic arteries and arterioles in a segmental fashion. All layers of the vessel wall are involved. The veins rarely are involved. The early lesions consist of alterative degenerative changes in the media, manifested by edema and a thready fibrinous exudate containing a few leukocytes, so-called fibrinoid degeneration. This is followed by the acute inflammatory stage, in which there is infiltration of the media and adventitia with polymorphonuclear leukocytes with occasional eosinophils, lymphocytes and plasma cells. This results in necrosis of the media and elastic interna, which becomes stretched and fragmented. This marked subendothelial reactive proliferation results in

TABLE I

Organs Involved in 230 Cases of Essential Polyangiitis
(Armed Forces Institute of Pathology)

	No. Cases	Percentage
Kidney	165	72
Heart	134	58
Adrenal	118	51
Pancreas	116	50
Gastrointestinal Tract	109	47
Liver	96	42
Spleen	85	37
Testis	61	26
Lungs	53	23
Skeletal Muscles	37	16
Gall-bladder	36	16
Brain	33	14
Miscellaneous	47	20

occlusion of the vessel by secondary thrombosis. This thrombus may be recanalized, or infarction of end organs may ensue. The weakened vessel wall may give way, with aneurysmal dilatation, rupture and hemorrhage. This stage is followed by marked proliferation of fibroblasts from the adventitia into the inflammatory zone, accompanied by a reduction of polymorphonuclear leukocytes, with an increase in lymphocytes and plasma cells. This may be followed by the healing stage, in which there is thickening of the vessel wall due to intimal proliferation, and subintimal, medial and periadventitial fibrosis.

Arkin [3] stated that arteries were involved as follows: renal, 80 per cent; coronary, 70 per cent; hepatic, 65 per cent; gastrointestinal tract, 50 per cent; mesenteric, 30 per cent; muscle, 30 per cent; pancreas, 25 per cent; peripheral vessels, 20 per cent; and cranial, 8 per cent. Middleton and McCarter [62] stated that arteries were involved in the following order: renal, coronary, mesenteric, hepatic, arteries to other viscera, cranial and peripheral. We found that, in the 230 cases studied at the Armed Forces Institute of Pathology, arteries were involved in the following order: renal, coronary, adrenal, pancreatic, mesenteric, hepatic and splenic, as shown in table 1.

The disease process of the blood vessels resulted in multiple infarction of the kidneys, myocardium, spleen and liver, as shown in table 2.

TABLE II

230 Cases of Infarction in Essential Polyangiitis
(Armed Forces Institute of Pathology)

	No. Cases	Percentage
Kidney	71	31
Myocardium	40	17
Spleen	37	16
Liver	35	15
Lungs	24	10
Testis	20	9
Adrenal	16	7
Gastrointestinal Tract	14	6
Pancreas	13	6

Clinical Features

The clinical manifestations of essential polyangiitis in 607 cases (177 cases reviewed by Harris, Lynch and O'Hare,[29] 200 cases from the English literature, and 230 cases from the Armed Forces Institute of Pathology) are listed in table 3.

The clinical manifestations of essential polyangiitis are determined by the constitutional symptoms and by the impaired blood supply to the various organs. The common constitutional symptoms are fever, chilliness, tachy-

Table III

Clinical Manifestations in 607 Cases of Essential Polyangiitis

	Harris 177 Cases %	Mowrey 200 Collected Cases %	Mowrey 230 Cases AFIP %	607 Cases %
Leukocytosis	73	75	69	72
Fever	81	66	63	68
Abnormal Urinalysis	65	74	64	67
Hypertension	53	59	62	58
Anemia	48	55	58	54
Weight Loss	44	52	53	51
Musculoskeletal	47	64	43	50
Abdominal Pain	56	53	38	48
Weakness	45	49	45	46
Gastrointestinal Symptoms (Other Than Pain)	33	53	48	45
Tachycardia	48	42	45	45
Peripheral Neuritis	49	39	35	42
Edema	49	33	30	38
Pulmonary Symptoms	40	46	26	36
Azotemia	13	29	37	27
Skin Manifestations	27	40	12	25
Central Nervous System Symptoms	26	20	26	24
Hepatomegaly	0	20	23	21
Eosinophilia	33	18	7	18
History of Allergy	21	14	3	12
Icterus	12	11	12	12
Lymphadenopathy	11	9	10	9
Impaired Liver Function Tests	0	1.5	10	6

cardia, leukocytosis and anemia. Compromise in the blood supply results in hypertension, disturbed renal function, cardiac failure, abdominal pain, muscle atrophy, peripheral neuritis, ulceration or gangrene of the bowel.

Fever was low grade, continuous or intermittent. It frequently was septic and out of proportion to the patient's clinical appearance. It occurred in 68 per cent of the cases. Prolonged afebrile periods were not uncommon. Frank chills were uncommon but chilliness was frequent. The tachycardia was usually out of proportion to the temperature. Polymorphonuclear leukocytosis was the most common manifestation, occurring in 72 per cent of the cases, and was apparently unrelated to the degree of fever. Eosinophilia was not common unless there was an associated allergic manifestation such as asthma. Eosinophilia as high as 84 per cent has been

reported by Wilson and Alexander [98] who, in a study of 300 cases of periarteritis nodosa, found that 18 per cent had asthma. Ninety-four per cent of the latter had an associated eosinophilia; the incidence of eosinophilia in the remaining cases was only 6 per cent. We found an over-all incidence of eosinophilia of 18 per cent. The majority of patients had a secondary anemia which was quite marked.

Boyd [9] found an incidence of neuromuscular symptoms, exclusive of arthralgia, in 129 cases. We found an incidence of 64 per cent in our series collected from the literature. Arthralgia, polyneuritis and myositis were found. The polyneuritis was usually asymmetrical. Pain, weakness, nerve trunk or muscle tenderness, paresthesia, hyperesthesia, followed by hypesthesia and patchy anesthesia, diminution or loss of tendon reflexes, and muscle atrophy were common.

The neurologic symptoms of periarteritis were usually due to a peripheral neuritis; however, the central nervous system alone was involved in approximately 8 per cent of the cases. Brenner [10] reported central nervous system involvement in 17 out of 55 patients. Involvement was manifested by psychiatric disturbances, meningitis, convulsions, vertigo, speech difficulties, encephalitis, paralysis of the external muscles of the eye, and acute ascending Landry's paralysis.

The kidneys were involved in 72 per cent of the 230 cases at necropsy, chiefly infarction, aneurysm and glomerulonephritis. Urinalyses were abnormal in 64 per cent. These abnormalities were proteinuria, cylindruria and hematuria. Functional tests revealed increasing oliguria, fixation and lowering of specific gravity, decreased phenolsulfonphthalein excretion and progressive azotemia.

We found the coronary arteries involved in 58 per cent of the 230 cases, compared with an incidence of 60 per cent according to Boyd,[9] yet angina pectoris was rare. Myocardial infarction occurred and resulted in sudden death in some patients. Electrocardiographic abnormalities included low voltage, inverted T waves, ST-T changes, and bundle branch block. Tachycardia out of proportion to temperature elevation was a common finding. Cardiomegaly due to hypertension was common, with resultant nondiagnostic cardiac murmurs. Pericarditis and hemopericardium have been noted. Congestive heart failure was the most common cause of death.

Abdominal symptoms were frequently the presenting complaint. Of Boyd's series, 168 had abdominal symptoms [9]; 53 per cent of our collected series had abdominal pain, but only 38 per cent of the Armed Forces Institute of Pathology cases. Many patients have had laparotomies for suspected appendicitis, cholecystitis and peptic ulcer. The abdominal symptoms were pain, usually aching or cramping in character, in the right upper quadrant or epigastrium, nausea, vomiting, anorexia, diarrhea, constipation and melena. Abdominal tenderness, hepatomegaly and icterus were not uncommon findings.

Skin manifestations were not uncommon. Alkiewicz [2] reported 36 patients with skin involvement, to which Ketron [36] added 23 more. McCall and Pennock [59] reported skin lesions in 27 patients. Harris [29] reported subcutaneous nodules in 23 per cent of 177 patients. We found skin manifestations in 40 per cent of our collected cases, but in only 12 per cent of the Armed Forces Institute of Pathology cases. The common skin manifestations were livedo racemosa, subcutaneous nodules, purpura, petechiae and urticaria. Hemorrhage, ulceration and gangrene occurred. Livedo racemosa was characterized by livid, arborescent, branched skin markings which shaded into the surrounding skin without sharp demarcation, and was commonly found on the nates and thighs and over the olecranon process. Subcutaneous nodules were usually 4 to 12 mm. in size and varied in number. They occasionally occurred in crops. The overlying skin was normal, translucent, edematous, or displayed red or violet discolorations. Nodules commonly were found on the forearms, chest, legs, abdomen, thighs, face, ankles, back, fingers and toes.

The pulmonary arteries seldom were involved; however, Spiegel [86] found such involvement in five out of 17 patients. We found pulmonary involvement in 53 out of 230 cases. Bronchopneumonia, pulmonary infarction, atelectasis and pleurisy were noted. Some authors suggest that Loeffler's syndrome and tropical eosinophilia are manifestations of essential polyangiitis. Transient infiltrations have been noted on x-ray films of the chest. Cough, dyspnea, pleuritic pain, hemoptysis and cyanosis have been noted by various authors, and were found in our cases.

Ocular manifestations have been noted by many observers. Paralysis of ocular muscles has been referred to. Neuroretinitis (papilledema, edema of retina, hemorrhage and AV nicking) is very common, but is not diagnostic. Sampson [76] believes the diagnosis may be made by the characteristic finding of multiple and exudative retinal detachment, perivascular hillocks of pale choroidal exudate resembling miliary tubercles, and irregularity in the caliber of the retinal vessels.

Essential polyangiitis with its protean clinical manifestations is frequently unrecognized ante mortem. It has been confused with trichinosis, typhoid fever, cholecystitis, appendicitis, dysentery, meningitis, encephalitis, tuberculosis, polymyositis, peripheral neuritis, rheumatoid arthritis, gastroenteritis, septicemia, acute nephritides and nephrosclerosis, to mention a few of the more common errors.

Hepatic Manifestations

Essential polyangiitis involves the liver in 65 per cent of the cases, according to Arkin.[3] Ninety-six (or 42 per cent) of the 230 cases in the files of the Armed Forces Institute of Pathology had hepatic involvement, yet only a few of these presented clinical manifestations of hepatic disease, except terminally. We wish to report two patients of our own, plus 14

among the 230 cases at the Armed Forces Institute of Pathology who were thought to have primary hepatic disease.

Case Reports

Case 1 (PJAH). A male, 40 years of age, was well until March, 1951, when he noted the onset of malaise, left shoulder pain, anorexia, nocturia, urinary frequency and dysuria, followed by edema of the feet, hands and eyes, abdominal pain, and increasing pain in both feet. He was admitted to an overseas hospital, where he was found to have a blood pressure of 130/95 mm. of Hg, hepatomegaly, abdominal tenderness, ankle edema, and telangiectasia over the thorax, back and upper legs. During his hospitalization there he had a low grade fever and lost 20 pounds. Urinalysis revealed persistent proteinuria, hematuria and pyuria. Urine culture yielded hemolytic *Staphylococcus aureus*. There was no anemia or leukocytosis; erythrocyte sedimentation rate was 27 mm. per hour. Liver function tests, i.e. serum bilirubin, bromsulphalein, cephalin flocculation, serum protein, alkaline phosphatase and prothrombin times, were within normal limits. Thymol turbidity was 10 units. Histologic study of the liver obtained by needle biopsy revealed periportal fibrosis, with scant lobular distortion interpreted as portal cirrhosis.

He was admitted to Percy Jones Army Hospital on December 3, 1951, with general malaise, myalgia, arthralgia, crampy midabdominal pain, low back pain, nocturia, urinary urgency and frequency, dysuria and anorexia. On physical examination he was found to be a chronically ill, emaciated individual with a blood pressure of 165/120 mm. of Hg. Arterio-venous nicking was noted in the ocular fundi. He had sinus tachycardia, hepatomegaly palpable 3 cm. below the right costal margin, generalized lymphadenopathy, petechiae in the left axilla, diminished knee and ankle reflexes on the right side, and marked hyperesthesia of both feet. Erythrocyte counts varied from 3.7 to 4.3 million, hemoglobin from 10.1 to 12.4 gm., and leukocyte counts from 5,000 to 11,000, with a normal differential count. Multiple urinalyses revealed hyposthenuria, persistent proteinuria, microscopic hematuria, pyuria and cylindruria. Phenolsulfonphthalein excretion was 30 per cent in two hours; urea clearance was 66 per cent of average normal; urine cultures were negative. A glucose tolerance curve was diabetic in type, but urinalyses were repeatedly negative for reducing substance. Serum albumin was 2.0 gm. per 100 c.c., and serum globulin was 2.5 gm. Nonprotein nitrogen was 44 mg. per 100 c.c.; serum bilirubin varied from 0.4 to 0.6 mg.; cephalin flocculation was 2 plus in 48 hours, thymol turbidity was 4 units, bromsulphalein retention was 18 per cent in 48 minutes; spinal fluid examination was within normal limits; cardiolipin microflocculation was negative; bone marrow was normal. Agglutinations for typhoid, paratyphoid, brucella and proteus OX19 were negative. Two determinations of the basal metabolic rate were plus 30 and plus 31 per cent. Protein-bound iodine was 5.2 gamma per 100 c.c. The patient's hospital course was progressively downward, with daily temperature of 100° F., persistent tachycardia and diastolic hypertension. Repeated electrocardiograms revealed nonspecific ST-T abnormalities, left heart strain and myocardial damage. Several tracings revealed paroxysmal auricular flutter and, on one occasion, irregular AV block. Histologic study of a muscle biopsy, taken shortly after admission, revealed essential polyangiitis. During the second month of hospitalization the patient developed irregular, fleeting pulmonary infiltration, visualized roentgenographically, in both upper lung fields. His neuropathy increased until he became bedridden. There were increasing edema and hepatomegaly. The patient died with intractable congestive heart failure, 13 months after the onset of his illness.

Autopsy, by Lt. Colonel Frank A. Mantz, MC, revealed typical healing and healed lesions of essential polyangiitis of the arterioles and small arteries of the

kidney, heart, liver, gastrointestinal tract, pancreas, testes, brain, spleen, lymph nodes and lungs. There were multiple pulmonary emboli, with infarction secondary to a mural thrombus of the right auricular appendage, myocardial fibrosis and multiple infarcts of the brain. The lobular architecture of the liver was distorted. The central veins were dilated with fibrous thickening of their walls. Extensive polygonal cell degeneration with fibrous replacement in the central areas extending outward in stellate fashion to the portal zone produced diffuse scarring throughout the liver. There was marked fatty metamorphosis. The bile canaliculi were distended with bile thrombi; the sinusoids were markedly dilated; the portal areas displayed irregular widening and fibrosis, with extensive bile duct proliferation and diffuse hyperplastic sclerosis; there was luminal narrowing of arterioles and arteries, with occasional recanalization of thrombi. This was interpreted as showing severe fatty metamorphosis, chronic passive congestion, severe cardiac cirrhosis with bile retention, and healed essential polyangiitis.

Case 2 (PJAH). A male, 24 years of age, was admitted to an overseas hospital on May 27, 1952, because of malaise, lassitude, chills, fever, night sweats, back pain, anorexia, a weight loss of 15 pounds, and easy fatigability, all of three months' duration. He had been treated during this time with various antibiotics and chemotherapy. Examination revealed only generalized adenopathy. Hemograms, urinalyses, febrile agglutinations, blood and urine cultures, intravenous pyelography, gastrointestinal x-ray series, chest x-rays, electrocardiograms and bone marrow examinations were within normal limits. Liver function tests were normal except for mild bromsulphalein retention. The erythrocyte sedimentation rate was elevated. A diagnosis of malignant lymphoma, Hodgkin's type, was made from a biopsy of a cervical lymph node.

The patient was admitted to Percy Jones Army Hospital on June 28, 1952, where physical examination revealed an emaciated male with a blood pressure of 106/62 mm. of Hg, hepatomegaly palpable 4 cm. below the costal margin, increased splenic dullness to percussion, and generalized lymphadenopathy. No other abnormalities were noted. Laboratory studies were within normal limits except for a leukocyte count of 12,000, bromsulphalein retention of 12 per cent, and a thymol turbidity of 9 units.

During his early hospitalization he had a daily diurnal temperature elevation to 102° F., and continued to lose weight. Review of the cervical lymph node biopsy did not support the diagnosis of Hodgkin's disease. He became afebrile and was granted a 30 day convalescent leave. On his return to the hospital on August 15, 1952, he had gained five pounds in weight. A liver biopsy at this time revealed a mild subacute nonspecific hepatitis. He was granted another 30 day leave, and upon return to the hospital complained of lower abdominal distress, weakness, jaundice, dark-colored urine, and a cough productive of mucoid sputum. Physical examination now revealed jaundice and abdominal tenderness in the right upper quadrant. Leukocyte counts varied from 20,000 to 46,000, with neutrophilia and toxic granulation. Urinalyses remained normal. There was 50 per cent bromsulphalein retention in 45 minutes; serum bilirubin was 7.5 mg. per 100 c.c.; alkaline phosphatase was 15.8 SJR units; thymol turbidity was 5 units, and cephalin flocculation was 2 plus in 48 hours. There was increased urinary urobilinogen excretion. At this time, biopsy of the liver revealed active chronic hepatitis, with early cirrhosis of the postnecrotic type and chronic pericholangitis. He was placed on a regimen of rest in bed, a high carbohydrate-high protein diet, multivitamins and, in addition, cortisone and Terramycin. There was marked subjective and objective improvement, with reversal of many of the laboratory findings on this regimen; however, he continued to have marked leukocytosis. After improvement for approximately two weeks he had a relapse and became progressively worse. At this time, he was thought possibly to have malignancy of the liver or marked postnecrotic cirrhosis. A third

liver biopsy, performed with difficulty because of the increased hepatic consistency, revealed pericholangitis and questionable cirrhosis, with a single vascular lesion classified as active essential polyangiitis. Early in December, 1952, he developed dyspnea at rest, palpitation, gallop rhythm, cardiomegaly, pulmonary edema, elevated venous pressure and prolonged circulation time, without peripheral vascular collapse. From December 8 to 11 there was a precipitous fall in hemoglobin to 7.6 gm. and the erythrocyte count to 3,000,000, with marked reticulocytosis. Urinalyses now revealed hyposthenuria, proteinuria, microscopic hematuria, pyuria and cylindruria. There was progressive azotemia. On December 14, he developed marked cyanosis and venous distention, limited to the head, upper extremities and thorax, extending to the level of the umbilicus. P_2 became markedly accentuated. A grade II systolic murmur was audible at the apex. The liver became enlarged, extending to the umbilicus, and a loud friction rub could be heard over the left lobe of the liver. An electrocardiogram revealed only sinus tachycardia and slightly delayed activation of the right side of the heart. The nonprotein nitrogen was 131 mg. per 100 c.c.; the creatinine was 1.8 mg. Edema, venous distention and cyanosis became generalized. The patient died suddenly, 10 months after the onset of his illness.

Autopsy, performed by Lt. Colonel Frank A. Mantz, MC, revealed diffuse essential polyangiitis involving the arteries and arterioles of the lungs, heart, liver, gastrointestinal tract, kidneys, pancreas, brain, peripheral nerves and skeletal musculature, resulting in thrombi and multiple infarcts of the liver, kidneys, brain, pituitary, testes, myocardium, lungs and spleen. There was a recent thrombosis of the left coronary artery secondary to essential polyangiitis with massive infarction of the right and left ventricles. There was a hemoperitoneum due to rupture of an aneurysm of the artery to the vermiform appendix. The liver weighed 2,475 gm. There was extensive perihepatitis with multiple irregular wedge-shaped hemorrhagic infarcts. The portal areas were distinct, containing conspicuous thick-walled blood vessels. Within some of these, extensive and organized thromboses had occurred. Microscopically, there was seen marked atrophy of the polygonal cells, marked dilatation of central veins, and extensive atrophy with necrosis of the central portion of lobules. The hepatic cells had indistinct margins; their cytoplasm was coarsely granular and, in areas, appeared coagulated with the formation of Councilman-like bodies. The nuclei were irregular and somewhat bizarre in appearance. There was moderate karyolysis and karyorrhexis, and many binucleated cells with nuclear hyperchromatism. There was moderate fatty vacuolation and glycogen depletion. There was widening of Disse's space; the Kupffer cells were enlarged and phagocytic. There was fibroblastic proliferation in the portal areas and proliferation of bile ducts. An occasional small adenomatoid nodule of regenerating hepatocellular tissue was seen. Many of the portal veins contained organizing thrombi. The hepatic arterioles and small arteries displayed inflammatory lesions of subacute, chronic and healed essential polyangiitis. This was interpreted as chronic perihepatitis, multiple infarcts, severe chronic passive congestion, portal cirrhosis, postnecrotic type hepatitis, acute and chronic consistent with essential polyangiitis, and thrombosis of the portal vein radicles. *Trichinella spiralis* infestation was found in the diaphragm.

Case 3 (AFIP).* A 59 year old male, a known hypertensive on a rice diet with previously normal liver function test, was admitted to a hospital with complaints of anorexia, vomiting, hiccough, jaundice and dark colored urine of one week's duration. Physical examination revealed icterus, hemangiomata, gynecomastia, cardiac enlargement, blood pressure of 200/120 mm. of Hg, and hepatomegaly. The erythrocyte sedimentation rate was 33 mm. per hour, with a normal hemogram. One-minute serum bilirubin was 9.4 mg. per 100 c.c., and the total serum bilirubin was

* AFIP: Armed Forces Institute of Pathology.

25.6 mg. Alkaline phosphatase was 15.6 SJR units; cephalin flocculation was 3 plus. There was increased urinary urobilinogen excretion. Serum albumin was 2.8 gm. per 100 c.c., and serum globulin, 3.4 gm. A diagnosis of regurgitation jaundice was made. The patient died on the twentieth hospital day. Necropsy revealed essential polyangiitis involving the liver, pancreas, adrenals, kidneys and seminal vesicles.

Case 4 (AFIP). A male, 57 years of age, was well until 1944, when he had pain involving the joints of the shoulders, wrists and ankles which lasted for one year. In 1946, he began having bouts of intermittent fever, profuse sweats, and joint pain lasting for two to three weeks at a time and occurring every two to three months. He was thought to have brucellosis and was treated with a vaccine which resulted in marked improvement lasting until March, 1948. He then developed jaundice, clay-colored stools, dyspnea, ankle edema, weakness, and a weight loss of 30 pounds, which resulted in hospitalization. Physical examination revealed stiffened joints, dependent edema, icterus, blood pressure of 110/72 mm. of Hg, hepatomegaly three fingerbreadths below the right costal margin, and absent knee jerks. The erythrocyte count was 3.6 million; hemoglobin was 9.9 gm.; leukocyte count was 10,500; serum albumin was 2.5 gm. per 100 c.c.; serum globulin was 3.2 gm.; cephalin flocculation was 3 plus; prothrombin time was 58 per cent, and bromsulphalein retention was 5 per cent. His condition became progressively worse, with fever, dyspnea, orthopnea, auricular fibrillation, and death three months after admission. The clinical diagnoses were portal cirrhosis, rheumatic arthritis and congestive heart failure. Necropsy revealed essential polyangiitis involving the heart, liver, pancreas, kidney, prostate and gastrointestinal tract.

Case 5 (AFIP). A male, 34 years of age, was admitted to an overseas hospital complaining of stiffness and pain in both legs, anorexia, fever and jaundice. The erythrocyte sedimentation rate was 38 mm. per hour; leukocyte count was 13,000; serum bilirubin was 2.7 mg. per 100 c.c.; cephalin flocculation was 2 plus in 24 hours; the urine urobilinogen was positive in a 1:80 dilution. He had an exploratory laparotomy to rule out subdiaphragmatic abscess, which was not found. He then was transferred to the United States with a diagnosis of acute infectious hepatitis after five weeks' hospitalization. He died suddenly while en route. Necropsy revealed essential polyangiitis involving the heart, gastrointestinal tract, liver, pancreas, kidneys, prostate, testes, brain, thyroid, adrenals and skeletal muscles, with multiple infarction of the kidneys, adrenals and pancreas.

Case 6 (AFIP). A male, 67 years of age, a known hypertensive, complained of weakness and increasing nocturnal cramping of both legs. He was hospitalized three months later for a period of two months for infectious hepatitis, hypertension, peripheral neuritis, and slight paralysis of the right arm and leg. He was noted to have a leukocyte count of 33,000, an enlarged, tender liver, a blood pressure of 190/135 mm. of Hg, and tachycardia. Two months after discharge from the hospital he was re-admitted to another hospital with dyspnea, cyanosis, profuse perspiration, a widened palpebral fissure (Dalrymple's sign), tachycardia, blood pressure of 260/100 mm. of Hg, anemia, enlarged liver and albuminuria. Liver function tests were normal except for an alkaline phosphatase of 13.2 SJR units. Death occurred five months after the initial onset, with the clinical diagnoses of chronic infectious hepatitis and pheochromocytoma. Necropsy revealed essential polyangiitis involving the lungs, heart, liver, pancreas, adrenals, kidneys, prostate, testes and brain. The adrenals showed adenomatous hyperplasia with necrosis and hemorrhage.

Case 7 (AFIP). A male, 50 years of age, was retired from the Army in February, 1947, because of cirrhosis of the liver. In September, 1947, he noted backache, right upper quadrant discomfort, nose bleed and vomiting. He was noted to have hepatomegaly, with a bromsulphalein retention of 19 per cent; the other liver function tests were within normal limits. His condition rapidly deteriorated, necessitating hospitalization on November 15, 1947. Upon admission he had icterus, spider

angiomata, gynecomastia, "hepatic palms," purpuric lesions of both ankles, hepatomegaly, splenomegaly, ascites, and a blood pressure of 130/90 mm. of Hg. He was thought to have decompensated portal cirrhosis. The purpuric lesions became nodular, and the additional diagnosis of Schoenlein-Henoch purpura was entertained. Death occurred on December 3, 1947. Necropsy revealed essential polyangiitis of the gastrointestinal tract, heart, lungs and liver.

Case 8 (AFIP). A male, 28 years of age, was vaccinated against yellow fever October 5, 1943, which was followed by generalized aching for two days. One week later he suddenly collapsed with abdominal cramps, anorexia, nausea, vomiting and jaundice. He was thought to have acute catarrhal jaundice and was treated with a hepatitis regimen. He developed progressive weakness, weight loss, emaciation, pains in the arms and legs, paresthesias, diminished deep tendon reflexes, a blood pressure of 176/126 mm. of Hg, erythrocyte sedimentation rate of 39 mm. per hour, leukocyte counts of 15,000 to 20,000, albuminuria and progressive azotemia. A muscle biopsy revealed essential angiitis. Death occurred seven months after the initial illness. Necropsy revealed essential polyangiitis involving the spleen, pancreas, kidneys, brain, heart, liver, esophagus, spinal cord and skeletal muscles. Death was due to an intracerebral hemorrhage in the right occipital lobe.

Case 9 (AFIP). A male, 30 years of age, was well until July 6, 1952, when he developed anorexia, abdominal cramps, night sweats, jaundice and dark colored urine, which resulted in his hospitalization on July 24. On admission to the hospital he had a leukocyte count of 22,450, an afternoon fever and evident weight loss. On July 31, he developed acute right upper quadrant pain with rigidity in the epigastrium. Diagnoses of liver abscess, portal cirrhosis, tuberculous peritonitis and abdominal Hodgkin's disease were entertained. His condition became progressively worse, with rapid development of hypertension, a blood pressure of 190/130 mm. of Hg, anemia, auricular fibrillation, acute myocarditis, congestive heart failure, azotemia, and a cerebral vascular accident. Death occurred two months after onset of his illness. Necropsy revealed essential polyangiitis involving the heart, kidneys, liver, pancreas, brain, testes, lungs, spleen, adrenals and skeletal muscles, with multiple infarction of the brain, testes, kidneys, spleen and myocardium.

Case 10 (AFIP). A male, 26 years of age, was well until December 4, 1945, when he developed anorexia, nausea, vomiting and jaundice. He was thought to have infectious hepatitis. He improved until January 30, 1946, when he developed oliguria, dependent edema, puffiness of the eyes, ascites, hematuria, albuminuria, cylindruria, and a blood pressure of 170/120 mm. of Hg. His condition rapidly deteriorated, with progressive azotemia, the nonprotein nitrogen rising to 273 mg. per 100 c.c. and creatinine to 10.7 mg. Death occurred three months after onset. Necropsy revealed essential polyangiitis involving the kidneys, urinary bladder and mesentery, in addition to a proliferating glomerulonephritis.

Case 11 (AFIP). A male, 22 years of age, was admitted to a hospital on June 29, 1942, with painful joints, anorexia, constipation, abdominal tenderness, generalized lymphadenopathy and jaundice of three days' duration. A diagnosis of catarrhal jaundice was made. Subsequently he developed a low grade fever, with leukocyte counts of 20,000 to 30,000, and began complaining bitterly of muscle soreness. On July 19 he developed excruciating pain in the right upper quadrant and shock, and died after a three weeks' illness. Necropsy revealed essential polyangiitis involving the heart, kidneys, liver, intestines and skeletal muscles, with multiple infarction of the myocardium, kidneys and liver. Death was due to a large retroperitoneal hemorrhage.

Case 12 (AFIP). A male, 60 years of age, was well until August, 1949, when he had an attack of nausea, vomiting, cramping right upper abdominal pain, and diarrhea lasting for five days. He had several similar attacks associated with a 30 pound weight loss until November 1, when he became jaundiced, with dark colored

urine and clay-colored stools. Upon admission to a hospital he had an enlarged, tender liver and reversal of the A-G ratio. The gall-bladder was not visualized by x-ray. A laparotomy revealed chronic cholecystitis and cholelithiasis. His post-operative course was uneventful except for a low-grade fever. He was discharged from the hospital on January 20, 1950, but was re-admitted on February 6 because of continued weight loss, colicky pain in the right upper quadrant, and melena. He was found to have marked tenderness in the right upper and left lower quadrants of the abdomen, dependent edema, erythrocyte count of 3.9 million, hemoglobin of 11.2 gm., erythrocyte sedimentation rate of 36 mm. per hour, occasional erythrocytes in the urine, a bromsulphalein retention of 10 per cent, serum albumin 2.1 gm. per 100 c.c., and serum globulin of 2.7 gm. He was thought to have a malignant growth, probably carcinoma of the sigmoid colon with metastases. Another exploratory laparotomy revealed gangrenous areas of the ileum and colon which were resected. Postoperatively, he developed gangrene of the scrotum, penis and lower extremities, with death seven months after the onset of his illness. Necropsy revealed essential polyangiitis involving the heart, spleen, liver, adrenals, kidneys, testicles, brain and gastrointestinal tract. There was infarction of the liver, left adrenal, left testicle, both kidneys and mesenteric thrombosis, with gangrene and perforation of the intestinal anastomosis resulting in purulent peritonitis.

Case 13 (AFIP). A male, 25 years of age, had fever, anorexia, abdominal cramping in the right upper quadrant and jaundice. He was noted to have hepatomegaly, ascites, generalized lymphadenopathy, pleural effusion, leukocyte count of 25,000, and increased urobilinogen excretion in the urine. He was thought to have acute hepatitis. Death occurred two weeks after onset of illness. Necropsy revealed essential polyangiitis involving the heart, liver, kidneys and adrenals, with infarction of the myocardium, liver and kidneys.

Case 14 (AFIP). A male, 59 years of age, was a mental patient with known hypertension and diabetes mellitus for many years. His terminal illness began in November, 1947, when he developed weakness, anorexia, abdominal pain, muscle pains, precordial pain and blood pressure of 190/120 mm. of Hg. The temperature varied from 101° to 102° F. There was a leukocyte count of 25,000, erythrocyte sedimentation rate was 40 mm. per hour, serum bilirubin was 1.8 mg. per 100 c.c.; bromsulphalein test revealed 45 per cent retention in 35 minutes. The liver was enlarged and tender. He was thought to have a hepatic abscess or carcinoma of the bile ducts. Death occurred suddenly after six weeks of illness. Necropsy revealed essential polyangiitis involving the liver, gall-bladder, urinary bladder, heart, kidneys, pancreas and esophagus, with multiple infarctions of the liver, myocardium, kidneys, pancreas, spleen and adrenals.

Case 15 (AFIP). A male, 53 years of age, had thrombophlebitis in 1940. Following this he complained of backache and various aches and pains, which were thought to be a conversion reaction. He was retired from the Army in 1946 with a diagnosis of portal cirrhosis. Liver function tests were normal in April, 1949. He was admitted to a hospital in July, 1949, where he was found to have a mottled bluish brown discoloration of both lower extremities, spider angiomata, hepatomegaly extending 6 cm. below the costal margin, blood pressure of 164/90 mm. Hg, serum bilirubin of 1.3 mg. per 100 c.c., serum albumin of 3.6 gm., serum globulin of 3.9 gm., bromsulphalein retention of 19 per cent, thymol turbidity of 16 units, thymol flocculation of 3 plus, and cephalin flocculation of 3 plus. There was increasing hypertension, with a cerebral vascular accident and death three weeks after the onset of terminal illness. Clinical impression was that of portal cirrhosis, malignant nephrosclerosis and acute hepatitis. Necropsy revealed acute, subacute and chronic essential polyangiitis involving the heart, brain, esophagus, stomach, small and large intestines, pancreas, adrenals, kidneys, prostate, testicles, gall-bladder and liver.

Case 16 (AFIP). A male, 25 years of age, was well until November, 1949, when he had anorexia, abdominal pain, weight loss, jaundice and dark colored urine. He was thought to have infectious hepatitis, from which he had apparently recovered by February, 1950. In May, 1950, he became ill with cough, fever, weight loss, diarrhea, anorexia, weakness, lethargy and listlessness, which caused his re-admission to a hospital. He was found to have a leukocyte count of 10,300 and a hemoglobin of 11.5 gm.; urine urobilinogen was positive in 1:320 dilution; bromsulphalein retention was 26 per cent. Other liver function tests were within normal limits. His hospital course was characterized by fever, abdominal cramping, nausea, vomiting, bloating and constipation. He was thought to have a subacute hepatitis; however, the diagnosis was changed to hepatic amebiasis because of the persistent leukocytosis, as high as 32,600, erythrocyte sedimentation of 34 mm. and a serum bilirubin of 10.5 mg. per 100 c.c., with bromsulphalein retention of 39 per cent. He was treated with emetine without avail. His condition rapidly became worse as he developed abnormal urinalyses and congestive heart failure, with death in July, 1950. He was thought to have hepatic necrosis with hepatorenal syndrome, or periarteritis nodosa. Necropsy revealed essential polyangiitis involving the kidneys, liver, heart, gastrointestinal tract, pancreas and testicles, with multiple infarction of the liver, kidneys, pancreas, testicles and gastrointestinal tract.

Discussion

Pathologic changes in the liver are similar to those found in other organs. The hepatic and/or cystic arteries, as well as, occasionally, the portal vein radicles, reveal the typical microscopic picture of essential polyangiitis. These changes may result in (1) aneurysm formation and rupture, (2) infarction of the liver, (3) "interstitial hepatitis," and (4) hepatic cirrhosis.

Infarction of the liver was noted in 35 of the 230 cases at the Armed Forces Institute of Pathology. Pass [68] collected 54 cases of infarction of the liver; 23 of these were due to periarteritis nodosa.

Christeller [15] has described an inflammatory infiltration consisting of leukocytes, lymphocytes and plasma cells in the periportal tissues adjacent to involved arteries which he called "interstitial hepatitis." These areas of infiltration are replaced by fibrous connective tissue with scarring extending into Glisson's capsule. So-called bile duct proliferation has been noted in addition. Menninga [62] stressed the importance of these findings and, in addition, described a peculiar calcification found in the periportal tissue. The increase in fibrous connective tissue apparently results in pressure atrophy and degeneration of the liver parenchyma. Menninga [62] emphasized that these changes are apparently specific for periarteritis nodosa, although there is a superficial resemblance to Laennec's cirrhosis. Many pathologists have noted these histologic changes, but most believe they are not diagnostic of essential polyangiitis.

Our cases 1 and 2 both showed evidence of extensive liver parenchymal damage in addition to vascular disease. Case 3 showed distortion of the lobular architecture, an increase in fibrous connective tissue and bile duct proliferation. There was also metaplasia of the liver cells to form bile duct epithelium. There was central lobular necrosis with polymorphonuclear

leukocytic infiltration. Case 6 revealed fibroblastic proliferation and lymphocytic infiltration into Glisson's capsule. There was pericentral atrophy of liver cord cells, periportal fibrosis and regenerating cord cells. In case 7 the liver architecture was markedly distorted. There were islands of liver parenchyma in which the central vein and portal areas were indistinguishable. There was fatty metamorphosis as well as generalized leukocytic infiltration. In case 15 the liver presented a cobblestone appearance. There were fibrous connective tissue proliferation, bile duct proliferation and lymphocytic infiltration. The liver cells were large and hyperchromatic with nuclear degeneration. In case 16 there was extensive destruction of the liver parenchyma due to infarction. However, areas not involved by acute infarction revealed disruption of the hepatic cords, and lymphocytic infiltration "identical to that seen in the chronic stage of hepatitis."

It is extremely interesting that, although the liver is commonly involved, there are few clinical signs or symptoms suggesting such involvement. Rupture of an aneurysm of the hepatic or cystic artery may have no symptoms referable to the liver until catastrophe occurs. Teacher and Jack,[91] however, believe that pain, jaundice, hemorrhage and fever suggest impending catastrophe due to rupture of an aneurysm.

The majority of reported cases of hepatic infarction have no symptoms suggestive of hepatic disease. Abdominal pain, particularly in the right upper quadrant or epigastrium, is common; however, this pain can be explained by involvement of organs other than the liver in the majority of cases.

In addition to pain there may be nausea, vomiting, fever and leukocytosis. This has led to exploratory laparotomy, cholecystectomy or appendectomy in a number of reported cases. Hepatomegaly was mentioned in approximately 20 per cent of the cases we reviewed from the literature and in 23 per cent of the Armed Forces Institute of Pathology cases. Icterus was reported in 11 per cent of our collected cases, and in 12 per cent of Harris' series and in the Armed Forces Institute of Pathology cases. Hepatomegaly and icterus are usually late and incidental findings, the majority of these being explained on the basis of terminal congestive failure.

Signs and symptoms suggesting hepatic disease are rare. We have found only 10 authenticated reports of essential polyangiitis masquerading as primary hepatic disease in addition to those reported above, as follows:

Verse[93]: An asthmatic male, 33 years of age, who had erysipelas followed by nephritis and pleuritis at 10 years of age, was admitted, 23 years later, with dyspnea, dependent edema, cyanosis, icterus, enlarged heart, an enlarged liver, which was hard with a roughened surface, tachycardia, fever, albumin and casts in the urine, and abdominal tenderness. The clinical impression was that of chronic nephritis, cardiac enlargement, cirrhosis of the liver and peritonitis. Autopsy revealed nephritic changes in the kidney, diffuse peritonitis due to perforation of the ileum secondary to thrombosis, and typical periarteritis nodosa of the mesenteric vessels. The liver revealed periportal fibrosis with multiple aneurysms of the hepatic artery.

Klotz [40]: Case 1, a female, 33 years of age, developed muscle and joint pain following a severe cold. This was followed by abdominal pain, fever, leukocytosis, albuminuria and icterus. There were tenderness and rigidity in the right upper quadrant, with a rapidly developing enlargement of the liver. She was thought to have cholecystitis, but died before surgery was attempted. Autopsy revealed typical lesions of periarteritis nodosa, with aneurysms and thromboses distributed along the hepatic and cystic arteries. One of these aneurysms had ruptured, resulting in extensive hemorrhage into the liver and into the peritoneum.

Case 2, a male, 53 years of age, was thought to have congestive heart failure. He had dyspnea, generalized weakness, cyanosis of the lips, icterus, cardiac enlargement, hepatomegaly, fever, tachycardia, albuminuria, cylindruria and anemia. Following acute tonsillitis he developed nodular purpuric spots. A diagnosis of congestive heart failure and Wilson's disease was made. Autopsy revealed typical periarteritis nodosa of the hepatic, cystic, pancreatic and mesenteric arteries, and arteries of the subcutaneous tissue, with aneurysms and thromboses of the affected vessels. The liver presented a picture of syphilitic cirrhosis. Death was due to intraperitoneal hemorrhage from rupture of an aneurysm of the gastrocolic artery.

Singer [82]: Case 1, a male, 29 years of age, had epigastric pain, jaundice, epistaxis, melena, anorexia, constipation, vomiting, cardiac enlargement, hepatomegaly, lymphadenopathy, hypertension of 200/140 mm. of Hg, leukocytosis, eosinophilia, anemia and albuminuria. The patient first was thought to have catarrhal jaundice or syphilitic hepatitis, and chronic nephritis. Later the patient was thought to have a duodenal ulcer associated with cholecystitis and peritonitis. He finally was operated upon, with a diagnosis of ruptured empyema of the gall-bladder into the duodenum. Following surgery, the patient was thought to have Henoch's purpura. The patient died three months later with progressive myocardial insufficiency and chronic nephritis. No autopsy was obtained; however, review of the surgical specimen revealed that the gall-bladder was filled with blood, while the wall contained numerous bluish red nodules which microscopically revealed aneurysmal dilatation of the arteries typical of periarteritis nodosa.

Case 2, a male, 57 years of age, had dyspnea, orthopnea, edema, cough, palpitation, tachycardia, elevated blood pressure to 200/100 mm. of Hg, cardiac enlargement, albuminuria, cylindruria and azotemia. He was thought to have nephritis with hypertension and myocardial insufficiency. He improved and was discharged from the hospital. On his third admission to the hospital he developed abdominal pain, jaundice, and a leukocyte count of 44,000, a nonfunctioning gall-bladder, bromsulphalein retention of 30 per cent in 30 minutes, and a van den Bergh of 2.5 mg. per 100 c.c. Autopsy revealed multiple infarcts of the liver and an enormously thickened cystic artery, an increase in periportal connective tissue, bile duct proliferation, and cellular infiltration, with the typical picture of periarteritis nodosa.

Arkin [3]: A male had a sudden onset of fever, severe icterus and acute nephritis, from which he apparently recovered after six weeks' hospitalization. Four years later he had epigastric pain, anorexia, weight loss, cardiac enlargement and an enlarged nodular liver. He soon developed edema, dyspnea and tachycardia, which did not respond to digitalis. Autopsy revealed "a small liver—hepar lobatum syphilitica." The surface was coarsely granular, with many depressed scars. The hepatic artery revealed obliterated thickened branches of healed periarteritis nodosa.

Spiegel [86]: A male, 72 years of age, had dyspnea, chest pain, epigastric pain radiating to the right upper quadrant, jaundice, acholic stools, weight loss, hepatomegaly, an icterus index of 55, azotemia and abnormal urinalysis. The patient was thought to have a malignant neoplasm with metastasis to the liver. Autopsy revealed an acute necrotizing arteritis, with polymorphonuclear infiltration of the liver, acute inflammation of the periportal spaces, bile thrombi, necrotizing arteritis of the gall-bladder, and gangrene of the right atrium.

Morgan [65]: A male, 44 years of age, had a history of lead poisoning, cyanosis and abdominal pain for one month. Blood pressure was 200/100 mm. of Hg. There were albumin, casts and sugar in the urine, secondary anemia, and an icterus index of 6. The patient had an exploratory laparotomy. Fat necrosis and a thickened, adherent gall-bladder were found. Death occurred on the fifth postoperative day. Autopsy revealed periarteritis nodosa with diffuse proliferative necrotic inflammatory and thrombotic arterial lesions, and multiple infarcts of the liver, gall-bladder, pancreas, brain and adrenals, chronic periportal hepatitis with parenchymal degeneration of the liver, chronic cholecystitis, chronic pancreatitis, myocardial degeneration and nephrosclerosis. The liver weighed 1,800 gm. There were multiple infarctions and cellular degeneration of the liver. The sinusoids were packed with polymorphonuclear cells and monocytes. The portal nodules were enlarged and fibrotic, resembling cirrhosis. Small branches of the portal vein were thrombosed and fibrotic. Chronic lesions were interspersed with acute lesions, resulting in fibrosis of the capsule, perilobular and intralobular fibrosis, and chronic interstitial hepatitis.

Teacher and Jack [91]: A male, 43 years of age, had edema, dyspnea, orthopnea, palpitation, weight loss, pain in the back and right upper quadrant, fever, systolic blood pressure of 230 mm. of Hg, cardiac enlargement, hepatomegaly without jaundice, albuminuria and cylindruria. Autopsy revealed a hemoperitoneum from rupture of an aneurysm of the hepatic artery due to periarteritis nodosa.

Madison [53]: A male, 53 years of age, was thought to have portal cirrhosis in 1940. In 1942 he had a massive gastrointestinal hemorrhage. In 1946 he developed hematuria, followed by rapid onset of cardiac failure, hepatomegaly and hemorrhagic nodules of the skin. Autopsy revealed portal cirrhosis with diffuse pancreatitis, and microscopically he was found to have had periarteritis nodosa.

Clinical hepatic manifestations of essential polyangiitis are apparently rare, although the liver is involved frequently when studied at necropsy. We have found only 10 authenticated reports in the literature, to which we have added 16 cases. There appears to be no doubt that involvement of the blood vessels may result in aneurysm with rupture and hemorrhage, or infarction of the liver. There can be but little doubt that disruption of lobular architecture, infiltration of leukocytes, lymphocytes and plasma cells into the periportal tissues, bile duct proliferation, and atrophy and degeneration of the liver parenchyma are found in many cases of essential polyangiitis. It is a moot point whether these changes are a direct result of the vascular lesion or whether they are coincidental findings. We believe, with Menninga and Christeller, that they are a result of the vascular disease. The rarity of reported clinical manifestations of hepatic disease is probably due to the well known fact that the liver has a great margin of safety, in that a large portion of it must be destroyed before there is clinical evidence of impaired liver function.

Summary

1. The clinical manifestations of 430 cases of essential polyangiitis (200 cases reviewed in the English literature since 1941, and 230 cases taken from the files of the Armed Forces Institute of Pathology) have been presented.

2. Twenty-six cases of essential polyangiitis masquerading as primary hepatic disease have been presented in detail.

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SOME REASONS FOR FAILURES IN REFERRAL FOR PSYCHIATRIC CARE OF PATIENTS WITH PSYCHOSOMATIC ILLNESSES *

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It is estimated that more than 50 per cent of patients with psychosomatic disorders fail to follow through on referrals for psychiatric treatment.

Experience over the past five years has aroused my interest in the problems of referral. These experiences were both in private psychiatric treatment of patients with psychosomatic disorders, and as psychiatric consultant to a university hospital psychosomatic seminar attended by the medical residents. Many colleagues, both internists and psychiatrists, agree that an overwhelming number of patients referred for psychiatric care because of psychosomatic illnesses do not make the initial contact with the psychiatrist. Further, they agree that only a very few patients—it is difficult to estimate how many—remain in treatment after the first several interviews.

We have tried to understand both some of the factors that tend to keep patients away from recommended therapy and some that seem to help patients seek and stay with psychotherapy. Only a few will be discussed here.

In general, patients with psychosomatic disorders seem to fall into two main groups in their experience with the referring physician. The patient in the first group has usually been seen by the physician for many months. The physician has done a complete physical examination, and has laboriously tracked down many of the complaints and investigated them in every possible way. Medication was first directed at the possible organic basis for the complaint and then, for many months and often years, the physician attempted symptomatic treatment for the ever-present complaints. The practitioner often finds that, with each new medication and his own enthusiastic hope that perhaps this time he will finally alleviate the patient's distress, the patient seems to respond for a few weeks. He returns to the doctor saying the symptoms are less disturbing, and he seems better. The physician suggests that the patient continue the medication and report back at infrequent intervals, and in a short time the patient's complaints are again full-blown. The physician, desperate, tries to find some other drug that might help. This circle of events occurs again and again until finally, in desperation, the practitioner suggests to the patient that, since various forms of treatment have not helped, his troubles are psychologic ones and a psychiatrist should be consulted. This patient almost never comes for psychotherapy unless

* Received for publication November 28, 1953.

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the symptoms are very painful and disabling. He usually finds another physician, to begin the same never-ending cycle, or he may respond to advertisements of promised miracle cures from nonmedical sources.

The patient in the second group comes to the physician with complaints that, during the course of investigation, the physician finds to be emotional in origin. The physician takes a detailed history, does a careful physical examination and the necessary laboratory work, and then, after spending several hours with the patient, sits down and explains in a careful way that these complaints are of emotional origin, and that the discomfort, pain and disability are no less than if there were organic pathology. He suggests that the person to help with the emotional problems is the psychiatrist. He makes the referral and is later surprised that in most instances the patient has made no contact with the psychiatrist or clinic. He finds also that, when the patient does see the psychiatrist, he often goes only once or twice and then discontinues treatment.

In the process of following the work of the medical residents in the psychosomatic clinic, and through closer attention to personal experiences with both successful and unsuccessful referrals, as well as through discussion with colleagues, certain common factors began to appear.

First, it became very clear that the medical resident and the practising physician generally were not aware that, by the time they had made a careful investigation and seen the patient several times, a relationship had begun to develop. That is, certain feelings of confidence, trust, liking and dependence had been vested in the doctor. Thus, when the physician suggested to the patient the need for psychotherapy, he failed to recognize the feelings of rejection in the patient often evidenced by his reluctance to accept the decision of his doctor. The patient may express his desire to continue his contact with his doctor and his uneasy feelings about talking to a strange physician by his query, Couldn't the doctor treat him himself? Some patients feel so rejected that they accept the recommendations with seeming alacrity in their haste to leave the office. It must be clear that other factors enter into this situation which we do not describe. (The physician's own preference with regard to spending time talking with patients; his ease or lack of it in such a situation; his feelings about the handling of psychosomatic disorders; that is, can psychotherapy be of help, are all important determinants of the patient's reaction to the referral.) It should also be noted that when the physician refers a patient to other specialists he usually retains the general management of the patient and continues contact with him. He usually relinquishes this general interest in the patient's well-being when he refers him to a psychiatrist.

We have thus begun to suggest that the physician clearly indicate continued interest in the patient when he makes the referral. He might ask the patient to return in several weeks to let him know how things are going in psychotherapy, or he may perhaps suggest that the patient might not find

the particular psychiatrist congenial and that the physician wants to hear by phone what his feelings are and how he is getting along. If he evidences continued interest in the patient, his ailments and complaints, until a relationship has been built up with the psychiatrist, this may mitigate the patient's feelings of being set adrift or rejected.

Often patients with psychosomatic disorders, on first appointment with the psychiatrist, seem quite angry and disturbed, and say such things as, "Dr. So-and-So sent me to you to be fixed up." The "do me something," "cure me now" attitude of many such patients seems to be greatly reduced (although not completely eliminated) by the continued interest of the referring physician. When the patient himself indicates, by less frequent phone calls or office visits, that he no longer needs this continued interest from the referring physician, a parting comment by the physician that, should the patient ever need further medical attention, he would be glad to see him, often ends this phase of the relationship cordially.

The above does not ignore the well known experiences of both internists and psychiatrists that many patients with psychosomatic illnesses are very suspicious of psychotherapy and difficult to work with even when they stay in therapy. Many patients would have nothing to do with psychotherapy if so labeled, and would not participate in such treatment in a psychiatric setting.

We have come to understand that some patients are sent for psychiatric help only as a last, often desperate resort, and long after the referring physician has come to the end of his wits and patience. The physician feels increasingly uncomfortable in the face of the incessant complaints, unsatisfied demands, and continued ill health of the patient, which remind him of his inability to help. The long duration of such doctor-patient relations may increase the feeling of rejection and anxiety of the patient when he is referred to a psychiatrist or psychiatric clinic. His hostile feelings at being thus disposed of and having a known, defined and important relationship disrupted may result in a disequilibrium for the patient and a frenzied hunt for someone, usually not a psychiatrist, to take the place of the former physician.

Although it is not directly germane to the central problem of this paper, we cannot resist commenting on the effectiveness of medical residents in the treatment (with some supervision) of patients with severe and chronic psychosomatic disorders. They evidence interest in the patient as a human being. They have the time to see their patients at regular intervals, and slowly they acquire the ability to listen attentively with reduced tension and with a minimum of interpretative comments. The resident's concern for his patient, his discomfort and disability begins to establish rapport. In many instances it is possible, after a time, to space the interviews further apart, until the patient may be seen at three, five or even eight week intervals, with continued feelings of well-being and increased adequacy of functioning.

Such patients are thus carried for several years and several generations of residents, with mutual benefit. It is clear to us that most of these patients would not accept referral to a psychiatrist, do not consider their interviews psychotherapy, and realize only that it helps greatly to talk to a doctor who is interested and who listens carefully, even though he does not offer as much advice as they might like.

It seems possible that some of the problems of referral for psychiatric care would not arise if the physician could set aside some time just to listen comfortably to these patients, and did not feel the need to "cure" the patient by active intervention. Often the physician can reassure the patient that his illness is not organic but primarily emotional and not in any way less painful or disabling. He might suggest that the patient try talking with the doctor about himself and his troubles, to discover whether this is helpful. Such an approach may often prove to be effective and can be very gratifying to the physician. He may see his patient, under his interested attention, feel better, work and continue to function more adequately, and need the doctor's support less frequently, until there are only occasional office visits during exacerbations of symptoms around disturbing and critical life events.

When the physician does feel that referral for psychiatric treatment is indicated, his continued interest in the patient until rapport with the psychiatrist has been established might increase both the number of patients who accept such referral and the number of patients who will stay in treatment beyond the initial interviews.

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HOW SAFE IS CATION EXCHANGE RESIN THERAPY WHEN USED IN PRIVATE PRACTICE? A CLINICAL STUDY AND PARALLEL LABORATORY STUDY *

By Charles William Smith, M.D., F.A.C.P., Kenneth E. Quickel, M.D., F.A.C.P., Arthur E. Brown, M.D., and Chester G. Thomas, M.D., *Harrisburg, Pennsylvania*

Most clinicians [1, 2, 3] who first investigated cation exchange resins to control edema tempered their enthusiasm for this therapy with precautions. Although they found that such resins removed sodium and thereby effectively reduced extracellular fluids, they recommended that patients taking them be followed with many chemical tests. Their precautionary recommendation appeared necessary because of the effect of the resins on electrolyte balance.

The following complications [1, 4, 5, 6, 7, 8, 9] have been noted in the literature. Acidosis, a not infrequent disturbance, was noted early in the use of resin therapy. These early resins exchanged hydrogen ions for the positive ions in the body, with a resultant loss of bicarbonate and the production of the clinical syndrome of acidosis. This was reported to be far more likely to occur in the presence of renal disease. Hypokalemia, hyponatremia and, to a lesser extent, hypocalcemia were also observed. Due to the removal of these ions by the changed resin, gastric and oral irritation due to the rapid exchange of the hydrogen ions in the upper gastrointestinal tract was also reported. These complications appeared to limit the safe use of exchange resins to hospitals and laboratories, where technicians were available for determining serum levels of sodium, potassium, calcium and carbon dioxide combining power.

Refinement in resin therapy saw the development of the so-called balanced resins, which exchanged ammonium and potassium ions instead of hydrogen ions. This refinement in resin therapy was designed to protect against the serious disturbances of electrolyte imbalance. However, many clinicians have felt reluctant to use resins without extensive laboratory control. If taken literally, these precautions would thus not only appear to demand facilities that the practicing physician does not always have available, but would also impose on the patient the cost of many laboratory tests. Because of these limitations, we used resins only when other treatments to mobilize fluids had failed. Later, as we treated more patients, it seemed that the need for controls had been over-emphasized. In the vast majority

* Received for publication July 3, 1953.
From the Harrisburg Clinic, Harrisburg, Pennsylvania.
Presented in part before the Postgraduate Institute of the American College of Physicians, Hahnemann Medical College, Philadelphia, May 13, 1952.

of our cases no serious complications from electrolyte imbalance had occurred.

Of course, we fully appreciated the fact that if these laboratory tests *are* necessary for safety, then the limitations imposed by cost, inconvenience and lack of laboratory facilities are necessary limitations. But this question occurred to us: What if some or all of these laboratory tests are *not* necessary? Then the precautions have overshadowed the beneficial results of cation exchange resin therapy. Consider that it reduces and in many cases eliminates the need for diuretics, and that it provides a measure of relief from the monotony of diets extremely low in sodium!

We decided, therefore, to determine whether cation exchange resin therapy can be used safely under conditions of private practice, that is, whether the therapy can be used without laboratory controls in treating patients who are not hospitalized. To do this, we did not depend merely on clinical signs to tell us of impending complications. Rather, we devised a method whereby, although both clinical and laboratory data were to be collected, the laboratory data were not to be revealed unless the clinical data had failed to forewarn.

Method

To simulate the physician in private practice, three of us followed the progress of the patients on resin therapy solely from a clinical standpoint. The "practitioners" examined the patients to record blood pressure, weight, pulse, edema (if present), and cardiac status; then they inquired about dyspnea, nausea and vomiting, abdominal pain, bowel habits, fatigue, and tolerance to resin. Although electrocardiograms and laboratory controls on blood, blood chemical tests * and a kidney function test were run on each patient (the tests and their frequency are shown in table 1), the findings were not made known to the practitioners but were reported to a "neutral" physician. If he observed that a complication that had not been recognized by the practitioner had begun to develop in a patient, he was to advise the practitioner of the impending risk.

Material

A total of 50 patients was placed on a regimen and studied for 12 weeks. Forty of these patients were chronically edematous and, of these, in 32 the edema was on the basis of cardiac disease. In two patients the edema was primarily the result of renal disease. Three were mixed cardiorenal cases, and in three the edema was of unknown etiology. The remaining 10 patients had severe hypertension without edema. The group of 50 included 32 patients with hypertension, 10 with arteriosclerotic heart disease, two with rheumatic valvular heart disease, three with edema of unknown etiology and one each with luetic heart disease, polycystic kidney disease and chronic

* This work was performed by the Johnston Laboratory, Harrisburg, Pennsylvania.

TABLE I

Laboratory Controls

	Weeks					
	1	2	5	7	8	12
Complete Blood Count	X			X		X
Sedimentation Rate	X			X		X
Hematocrit	X			X		X
Total Protein	X					X
Albumin	X					X
Globulin	X					X
Blood Urea Nitrogen	X	X		X		X
Sodium	X	X		X		X
Potassium	X	X		X		X
Electrocardiogram	X		X		X	X
Phenolsulfonphthalein	X					X
Mosenthal	X					X

Tests on urine analysis and titratable acidity of urine were run each week.

pyelonephritis. Two hypertensives had diabetes mellitus; one arteriosclerotic patient also had diabetes mellitus. There were 16 males and 34 females in an age range from 30 to 80 years, 80 per cent of the patients being over 50 years.

REGIMEN

After the first examination, we placed all patients on a diet designed to limit their sodium intake to 1 to 2 gm. daily, and on 15 gm. of resin three times a day. While on resin therapy the patients returned to the clinic once every week for reëxamination. The resin * used in this study consisted of a 3:1 mixture of the ammonium and potassium forms of a polycarboxylic cation exchange resin. This mixture, by replacing about 25 per cent of the ammonium salts with potassium salts, lessens the likelihood of acidosis and compensates, in part at least, for loss of potassium. The principle of ion exchange has been described (as has the clinical use of this form) by Dock and Frank [8] and by many others.

RESULTS

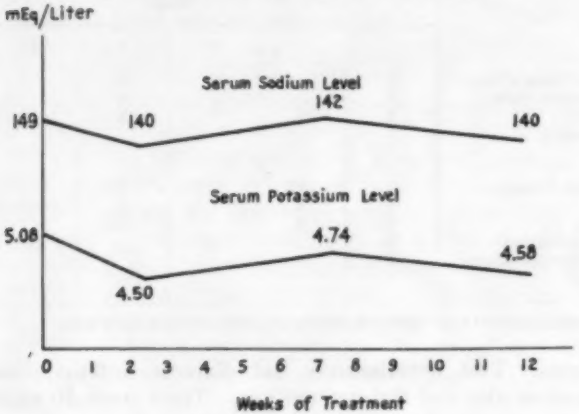
Fifty patients responded well to treatment with a cation exchange resin under conditions of private practice. Of this group, only three patients developed a complication which resulted from electrolyte imbalance. In no instance did the "neutral" observer find it necessary, on the basis of laboratory data, to warn any of the practitioners of an impending disturbance of electrolyte balance. In other words, the onset of this complication was apparent as readily from clinical signs as from laboratory data.

Of the three patients who developed a complication, two reported severe nausea and vomiting and showed signs of profound muscular weakness after

* Resodec, trademark of Smith, Kline & French Laboratories, Philadelphia.

TABLE II

Average Serum Sodium and Serum Potassium Levels of 50 Patients During 12 Weeks on Cation Resin Therapy



two weeks on resin therapy and sodium restriction. One patient presented a similar clinical picture after seven weeks of treatment. The practitioners who saw these patients started them immediately on oral doses of potassium chloride, 0.3 gm. four times daily and relaxed the restriction on their intake of dietary sodium: two patients were symptom-free in 24 hours, the other in 48 hours. A review of the laboratory data on these three patients showed that their serum potassium had fallen to an abnormal level.

The effect of cation resin therapy on the serum potassium and serum sodium levels of the group is given in table 2. It shows that levels of potassium and sodium decreased slightly during the first two weeks of resin therapy but then remained practically constant for the 10 subsequent weeks of treatment. No evidence of hyponatremia or acidosis developed; no significant change occurred in blood count, sedimentation rate and hematocrit determinations.

Studies on kidney function of these patients, including nine with kidney damage, revealed no significant change in the urine picture or in the blood

TABLE III

Blood Urea Nitrogen Levels (Mg. Per Cent) Typical of Group during 12 Weeks on Cation Resin Therapy

Patient	1	2	7	12
No. 4	18.3	17.4	19.4	14.2
No. 5	14.6	14.8	18.1	9.6
No. 8	14.9	11.8	8.4	10.5
No. 11	11.4	10.6	8.8	15.9
No. 15	10.5	10.6	16.4	17.0

TABLE IV

Characteristic Results from Mosenthal's Test after 12 Weeks of Cation Resin Therapy

	Patient No. 4				Patient No. 9				Patient No. 11			
	Initial		Final		Initial		Final		Initial		Final	
	c.c.	Sp.G.	c.c.	Sp.G.	c.c.	Sp.G.	c.c.	Sp.G.	c.c.	Sp.G.	c.c.	Sp.G.
8–10 a.m.	22	1.014	70	1.006	215	1.006	210	1.003	169	1.004	120	1.010
10–12 a.m.	—	—	90	1.007	285	1.007	100	1.017	39	1.009	124	—
12 noon–2 p.m.	126	1.006	75	1.008	185	1.007	205	1.007	145	1.003	125	1.010
2–4 p.m.	425	1.005	68	1.005	220	1.006	175	1.008	160	1.003	56	1.018
4–6 p.m.	243	1.004	150	1.003	208	1.006	115	1.012	199	1.005	70	1.023
6–8 p.m.	172	1.005	215	1.004	—	—	235	1.010	191	1.001	90	1.007
Total Day	988	—	668	—	1113	—	1040	—	903	—	585	—
8 p.m.–8 a.m.	662	1.006	500	1.006	858	1.004	950	1.017	102	1.006	855	1.007

urea nitrogen (BUN) levels during resin therapy. Results on BUN levels of five patients fairly typical of the group are given in table 3. Values from Mosenthal's tests show that, in general, the resin did not interfere with the patients' ability to concentrate urine. The results of the Mosenthal test on three patients representative for the most part of the series can be found in table 4. Results from phenolsulfonphthalein (P.S.P.) excretion tests during resin therapy varied. Patients with severe renal impairment before the study began showed the greatest decrease in P.S.P. excretion. The majority of patients, however, did not exhibit an abnormal decrease or a substantial increase over initial P.S.P. percentages while on the resin. Consequently, it seems that the decrease occurring in patients with renal damage is coincidental with resin therapy and is not a cause-and-effect relationship. Data on phenolsulfonphthalein excretion rates of 10 patients characteristic of the group are presented in table 5.

By titrating urine acidity of patients taking resins, we hoped to determine whether data from this simple procedure could be correlated with data developed from the more elaborate controls. We found no predictable correlation between them.

TABLE V

Initial (I) and Final (F) Phenolsulfonphthalein Excretion (Per Cent) Rates after 12 Weeks of Treatment with Cation Exchange Resins

Patients	No. 4		No. 5		No. 10		No. 11		No. 13		No. 16		No. 17		No. 18		No. 20		No. 24	
	I	F	I	F	I	F	I	F	I	F	I	F	I	F	I	F	I	F	I	F
15′		24		9	7	1	6	27		28	54	31	23	7		22	22	22	48	24
30′	31	18	30	16	4	3	39	16	40	22	20	18	12	5	38		26	15		22
60′	30	20	9	8	6	2	12	12	30	17	15	16	15	6	25	27	24	15	38	23
Total 2 hr.	61	63	39	34	17	7	58	56	70	68	90	66	51	19	53	50	73	53	86	70

We observed, as Feinberg and Rosenberg [6] had previously, that cation resin therapy decreases the patients' need for mercurial diuretics and, in many instances, eliminates the need for them. Patients who had required from one to three injections of a mercurial diuretic every week to control edema required no more than one or two such injections a month when on cation resin therapy. In some cases resin therapy produced a diuretic response in patients who were refractory to mercurial diuretics, digitalis preparations and salt restriction.

Effect of Cation Resin Therapy in Hypertension: Thirty-three hypertensive patients who had moderate to slight edema comprised part of our group of patients. When treated with resin therapy, 20 (66 per cent) of

TABLE VI

Effect of Treatment on Blood Pressure and Weight of Obese Hypertensives, 15 gm. of Cation Exchange Resin Three Times Daily for 12 Weeks

Patient	Age	Blood Pressure		Weight		Patient	Age	Blood Pressure		Weight	
		Before	After	Before	After			Before	After	Before	After
M. M.	53	190/110	140/92	136	119	E. H.	43	196/100	210/130	99½	105
E. T.*	62	250/110	184/100	200	178	W. H.	56	190/110	130/80	126	115
M. S.	49	230/100	176/90	172	162	S. S.	68	160/90	180/80	135	137
J. R.	25	170/100	136/90	210	194	C. S.	63	178/98	184/96	217	214
I. S.	70	240/110	180/100	161	151	N. W.	62	170/94	170/90	120	115
H. P.	52	190/100	160/94	156	156	S. M.	72	206/112	168/104	151	154
M. B.	52	240/100	194/120	192	192	G. M.	51	176/80	150/84	170	154
D. S.	74	230/90	190/80	149	148	C. E. S.	55	200/110	160/90	188	178
E. R.	53	200/100	240/132	164	156	C. H. K.	49	172/110	160/90	158½	154
C. M.	57	190/100	156/90	150	136	C. R.	40	210/120	190/100	159	147
W. T. H.†	56	220/130	190/110	161	158	M. B.	64	240/114	210/100	163	158
M. C.	72	180/120	150/80	200	186	E. R.	55	212/108	156/96	137	133
I. K.	61	170/90	150/80	158	157	C. W.	60	210/108	208/100	158	157
G. W.	56	160/80	140/70	158	138	A. M. T.	69	212/90	166/82	127	122
M. C.	49	150/100	130/80	155	159	A. U.	71	278/110	236/100	132	124
P. P.	66	150/80	180/90	191	199	R. J. P.	56	160/94	140/90	190	186
						G. K.	33	152/120	140/86	210	200

* Treated 10 weeks.
† Treated 7 weeks.

these patients showed a significant reduction in blood pressure. These results, shown in table 6, indicate that cation resin therapy can be a useful adjuvant in the management of edematous hypertensives.

Several of the hypertensive patients exhibited definite signs of myocardial damage, as evidenced by S-T segment and T-wave patterns in their electrocardiograms. It was interesting to note that in three of these patients there seemed to be some improvement in their electrocardiographic tracings following resin therapy, although their clinical status remained unchanged.

Patient Tolerance: In general, the patients tolerated the resin fairly well. Five patients (10 per cent) had to discontinue the regimen, although half of them complained of occasional nausea and gastric discomfort when they

first began the regimen. They complained also of loss of appetite. After two weeks of therapy, however, the patients became accustomed to the bulkiness of the resin and tolerated it better. Most of the patients decided, after they had tried taking the resin in various beverages, that they preferred to use water as the vehicle. The next most acceptable beverages were fruit juice and Coca-Cola; a few preferred milk. Four patients reported attacks of diarrhea while taking the resin; four others said they were constipated. The constipation which developed was readily controlled by the use of Kondremul or Metamucil.

Discussion

Our results demonstrate that the need for laboratory controls on patients taking cation exchange resins has been overemphasized. Although hypokalemia may result, it can be readily recognized through clinical symptoms, as shown by our procedure. This complication, controlled promptly by giving potassium salts, is the only evidence of electrolyte imbalance we observed in 50 patients on cation exchange resin therapy, 15 gm. three times a day for 12 weeks. Data from our studies on renal function revealed that resins did not impair renal efficiency, even in patients with kidney disease. On the basis of this investigation, we feel that the physician in private practice can safely employ cation exchange resin therapy without elaborate controls. It will suffice for him to reëxamine his patient once a week, a sound practice when one treats congestive heart failure.

By explaining the advantages of resin therapy to patients, we find that their acceptance of this medication is fairly good in spite of the gastric discomfort they experience when they first begin taking resins. Adjusting the daily dose, when necessary, and suggesting various beverages as vehicles for the resin will help the patient become adjusted to the regimen. Often a little encouragement will suffice. Of course, if vomiting, diarrhea or other untoward signs develop, resin therapy should be discontinued. Nevertheless, many patients experiencing these side effects can with a respite resume resin therapy. Of our original group, 22 patients have continued on resins for approximately 17 months without evidence of electrolyte disturbance.

Summary

In this study, we undertook to determine if cation exchange resins could be given safely by the physician in private practice to nonhospitalized patients without his maintaining elaborate laboratory controls on the patients for signs of electrolyte imbalance. To do this, one of us served as a "neutral" observer of the laboratory data on our patients taking resins, while three of us, without knowing the results of the laboratory tests attended these patients as "practitioners."

We treated 50 patients with a cation exchange resin, 15 gm. three times daily for 12 weeks. In only three of them did a complication (hypokalemia)

develop. No evidence of hyponatremia or acidosis developed; no significant change occurred in blood count, sedimentation rate and hematocrit determinations. From our experience thus far with this cation exchange resin we feel:

1. It is a therapeutic agent that can be administered safely to the ambulatory patient without elaborate laboratory controls, provided the patient is under periodic clinical observation.
2. It is definitely of value in the control of edema.
3. It greatly reduces the need for adjuvant mercurial therapy.
4. It is generally well tolerated by the patients. Although patients may at first find the resin unpalatable, only five patients discontinued the regimen.
5. It is a useful adjuvant in managing edematous hypertensives. Twenty of 33 hypertensives with moderate to slight edema showed a significant decrease in blood pressure while on cation resin therapy.
6. Though hypokalemia may develop, its onset can be recognized as quickly through clinical symptoms as by laboratory methods; hypokalemia is readily controlled by administering potassium salts.

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NEEDLE BIOPSY OF THE LIVER: AN APPRAISAL OF ITS DIAGNOSTIC INDICATIONS AND LIMITATIONS*

By MARTIN S. KLECKNER, JR., M.D., *New Orleans, Louisiana*

INTRODUCTION

IT is recognized that accurate information derived from a thorough history and physical examination is unparalleled in importance to diagnose adequately diseases of the liver, and that data obtained from various hepatic function tests and needle biopsy of the liver may afford supplementary diagnostic information.[1] In many cases of liver disease these tests have limited value, perhaps due to the complexity of the functions of the liver and their discrepancy with hepatic morphology. Tests of hepatic function designate a certain pattern rather than appraise true metabolic functions in liver disease.

Needle biopsy of the liver, when adequately performed, should cause the patient minimal discomfort and provide a reasonably informative specimen of liver, particularly if the pathologic condition of the liver is diffuse. The use of this technic has often spared the patient unnecessary laparotomy in cases of metastatic neoplasm or acute hepatitis. The most outstanding objection to needle biopsy is the inability to demonstrate focal or widely separated hepatic lesions.

MATERIAL AND METHODS

This report concerns 145 consecutive needle biopsies of the liver.† To determine the diagnostic value and limitations of needle biopsy of the liver, the clinical diagnosis was contrasted with the histologic interpretation of the biopsies of the liver. In all of these cases there was a specific indication for needle biopsy of the liver, such as indeterminate hepatomegaly, cirrhosis, chronic parenchymatous or obstructive jaundice, neoplasm, hemochromatosis and hepatitis. It was felt that this study might furnish practical information regarding the accuracy and diagnostic limitations of histologic studies of the liver obtainable by needle technic. The technic of needle biopsy was the same as has been reported elsewhere.[2-11] An adequate specimen of hepatic tissue was obtained in all cases by either the Vim-Silverman needle or the Stauffer modification. The latter needle has the distinct advantage of providing a punch biopsy of the liver measuring from 2.5 cm.

* Received for publication October 16, 1953.

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† Part of this work was accomplished while the author was a Fellow in Medicine, Mayo Foundation, Rochester, Minnesota.

to 3.5 cm. in length. The site of the needle biopsy was chosen from the results of the physical examination of the liver. If a palpably enlarged liver reached 3 cm. or more below the costal margin, a subcostal approach was employed. In other cases the intercostal route was selected. The specimen was then fixed in 10 per cent formalin. The tissue was stained routinely with hematoxylin and eosin solutions. When hemochromatosis was suspected, a Berlin blue stain was utilized.

Results

The histologic diagnoses obtained by needle biopsy of the liver in which this procedure was indicated and the pre-biopsy clinical diagnosis of 145 cases are summarized in table 1.

1. *Diagnosis of Indeterminate Hepatomegaly:* Histologic examination of the liver in this series of 46 cases disclosed 16 cases of fatty infiltration, 12 of normal hepatic tissue, six of chronic pericholangitis, five of chronic passive congestion, two of granulomatous hepatitis, two of nonfatty portal cirrhosis, two of hemochromatosis and one of a hepatoma.

Table I

Correlation of Clinical Diagnosis and Hepatic Histologic Diagnosis as the Result of Needle Biopsy of the Liver in 145 Cases

Clinical Diagnosis	Hepatic Histologic Diagnosis
1. Indeterminate hepatomegaly (46 cases)	Fatty infiltration (16)
	Normal (12)
	Chronic pericholangitis (6)
	Chronic passive congestion (5)
	Granulomatous hepatitis (2)
	Portal cirrhosis (2)
	Hemochromatosis (2)
	Hepatoma (1)
2. Portal cirrhosis (26 cases)	Fatty portal cirrhosis (9)
	Nonfatty portal cirrhosis (16)
	Hepatoma (1)
3. Metastatic neoplasm (23 cases)	Metastatic adenocarcinoma (17)
	Melano-epithelioma (3)
	Normal (2)
	Metastatic oat-cell carcinoma (1)
4. Chronic jaundice (21 cases)	
a. Primary biliary cirrhosis (14 cases)	Chronic pericholangitis with bile stasis (8)
	Chronic pericholangitis (3)
	Chronic pericholangitis with stasis and cirrhosis (2)
	Metastatic adenocarcinoma (1)
b. Obstructive jaundice (4 cases)	Bile stasis (4)
c. Postnecrotic cirrhosis (3 cases)	Hepatitis with bile stasis (2)
	Chronic pericholangitis with bile stasis (1)
5. Acute hepatitis (14 cases)	Hepatitis (14)
6. Hemochromatosis (4 cases)	Hemochromatosis (4)
7. Polycystic disease of the liver (1 case)	Polycystic disease of the liver
8. Banti's syndrome (1 case)	Portal cirrhosis
9. Sarcoidosis (1 case)	Granulomatous hepatitis
10. Miscellaneous (8 cases)	Granulomatous hepatitis (3)
	Lymphosarcoma (2)
	Follicular lymphoma (1)
	Miliary tuberculosis (1)
	Hemosiderosis (1)

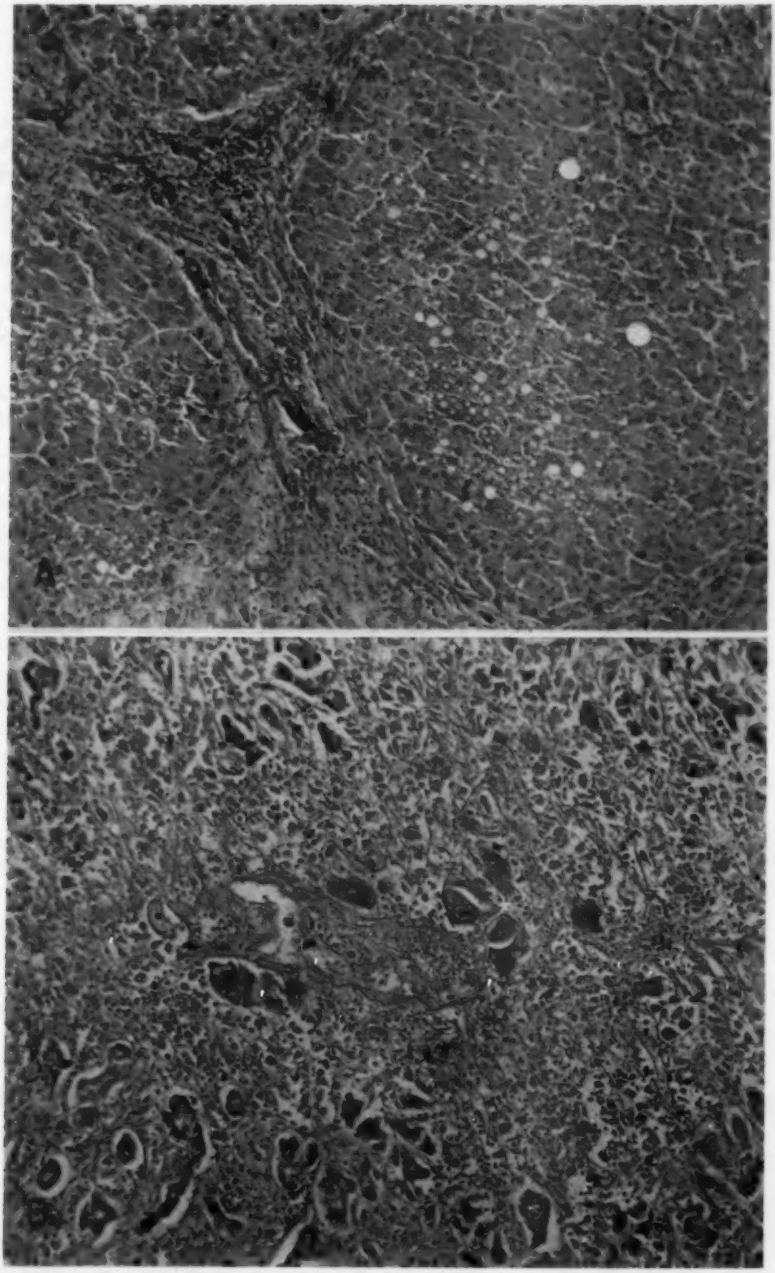


FIG. 1A (*above*). Portal cirrhosis: nodular regeneration, fibrosis, hepatic cellular damage and fatty infiltration. H & E × 60.
B (*below*). Hepatoma. H & E × 60.

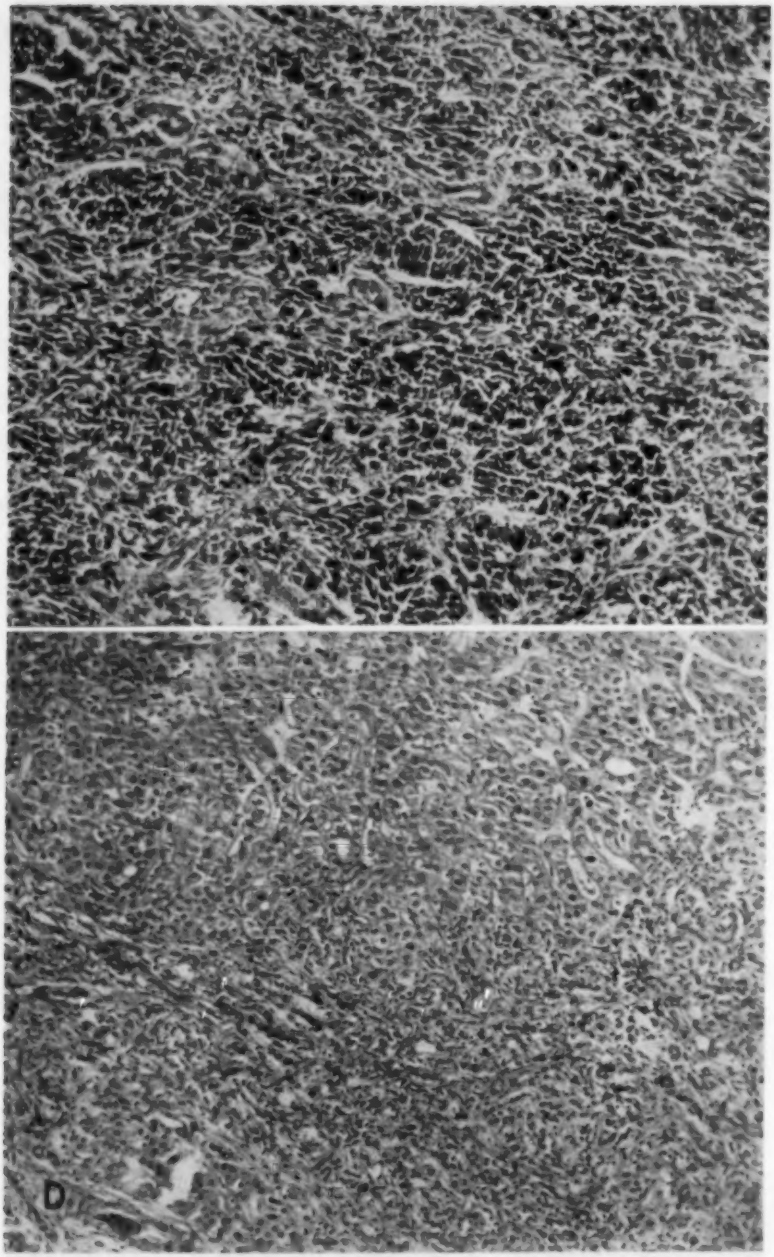


FIG. 1C (*above*). Metastatic melano-epithelioma of the liver. H & E × 60.
D (*below*). "Primary biliary cirrhosis" with xanthomatosis: chronic pericholangitis without stasis of bile. H & E × 60.

2. *Portal Cirrhosis:* Needle biopsy of the liver was performed in 26 cases with a clinical diagnosis of portal cirrhosis. Histologic examination of the hepatic specimens revealed 16 cases of portal cirrhosis, nine of portal cirrhosis with fatty infiltration (figure 1A), and one of a hepatoma (figure 1B).

3. *Metastatic Neoplasm:* Metastatic neoplasms of the liver were considered in 23 cases. Histologic examination of these biopsies revealed various cytologic stages of metastatic adenocarcinoma in 17 cases, melanoepithelioma in three (figure 1C), and a metastatic oat-cell carcinoma in one. Normal hepatic tissue was demonstrated in two cases.

4. *Chronic Jaundice:* There were 21 cases of various types of chronic jaundice. The clinical diagnosis of primary biliary (cholangiolitic) cirrhosis was established in 14 cases, four of which had xanthomatosis. Histologic examination of these hepatic biopsies revealed 13 cases of chronic pericholangitis (figure 1D), of which eight were cases with stasis of bile and two with both stasis of bile and cirrhosis (figure 2A). There were no distinguishing histologic features in the hepatic biopsies in these cases regardless of the presence or absence of xanthomatosis. A diagnosis of primary biliary cirrhosis was altered in one case when histologic examination of the needle specimen revealed a metastatic pancreatic adenocarcinoma. Biopsies of the liver in four cases of proved extrahepatic obstructive jaundice disclosed stases of bile in the biliary canaliculi, in the hepatic cells and in the portal spaces, together with the appearance, usually, of morphologically normal hepatic cells (figure 2B). Frequently, stasis of bile radiating like spokes of a wheel in the hepatic lobule was observed histologically in a hepatic specimen from a case of obstructive jaundice. Histologic examination of needle biopsies of the liver obtained from three cases diagnosed clinically as postnecrotic cirrhosis revealed two cases of hepatitis with stasis of bile and one case of chronic pericholangitis.

5. *Acute Hepatitis:* Diffuse degenerative and regenerative hepatic cellular changes, scattered foci of inflammatory cells, balloon-cells, proliferation of Kupffer's cells and, frequently, stasis of bile were demonstrated in the needle specimens obtained from 14 cases of acute hepatitis (figures 2C and 2D).

6. *Hemochromatosis:* Hemochromatosis was verified histologically in four cases by the concurrence of portal cirrhosis and abundant deposits of hemosiderin in the stroma, hepatic cells, Kupffer's cells, and epithelium of the bile ducts (figure 3A).

7. *Polycystic Disease of the Liver:* There was one case of polycystic disease of the liver, suspected clinically by the combination of hepatomegaly, normal hepatic function tests and polycystic kidneys. Histologic examination of the hepatic biopsy disclosed multiple cysts lined by cuboidal epithelium.

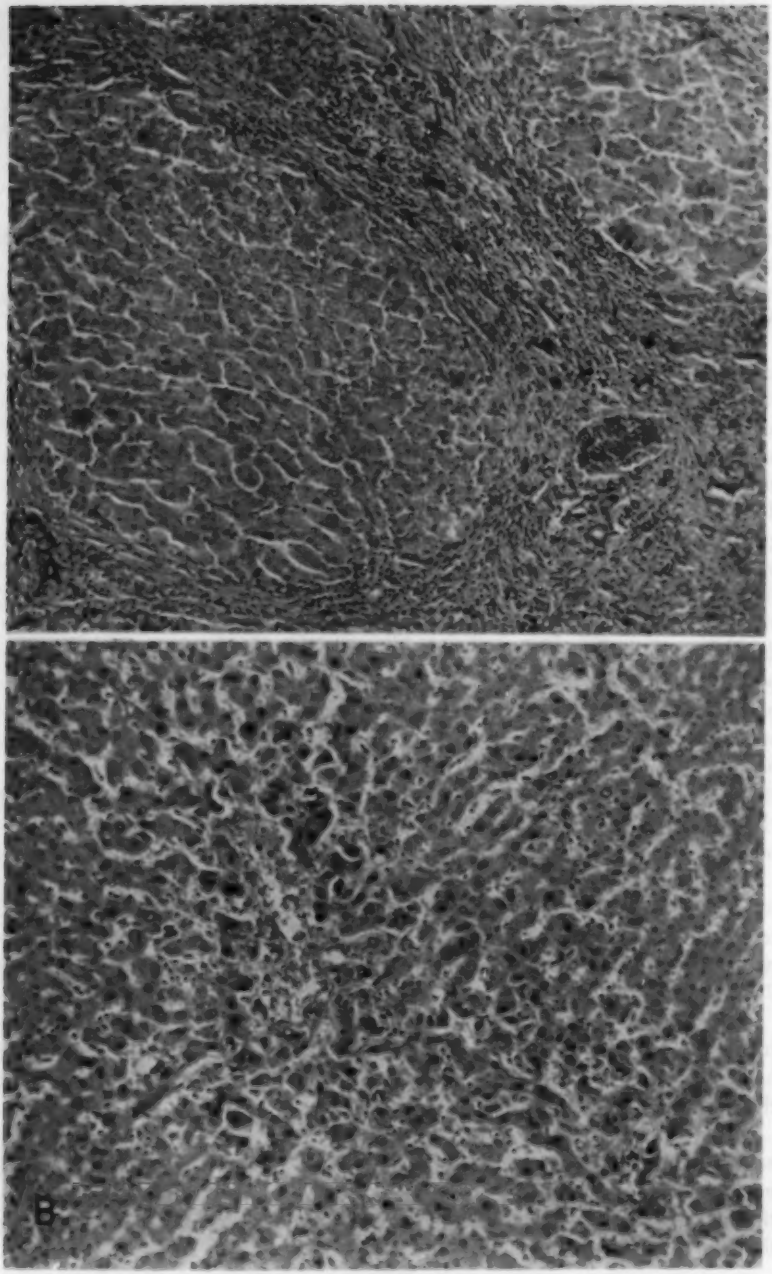


FIG. 2A (*above*). "Primary biliary cirrhosis" with xanthomatosis: chronic pericholangitis with stasis of bile and cirrhosis. H & E × 60.
B (*below*). "Obstructive jaundice": stasis of bile in bile canaliculi due to carcinoma of pancreas. H & E × 60.

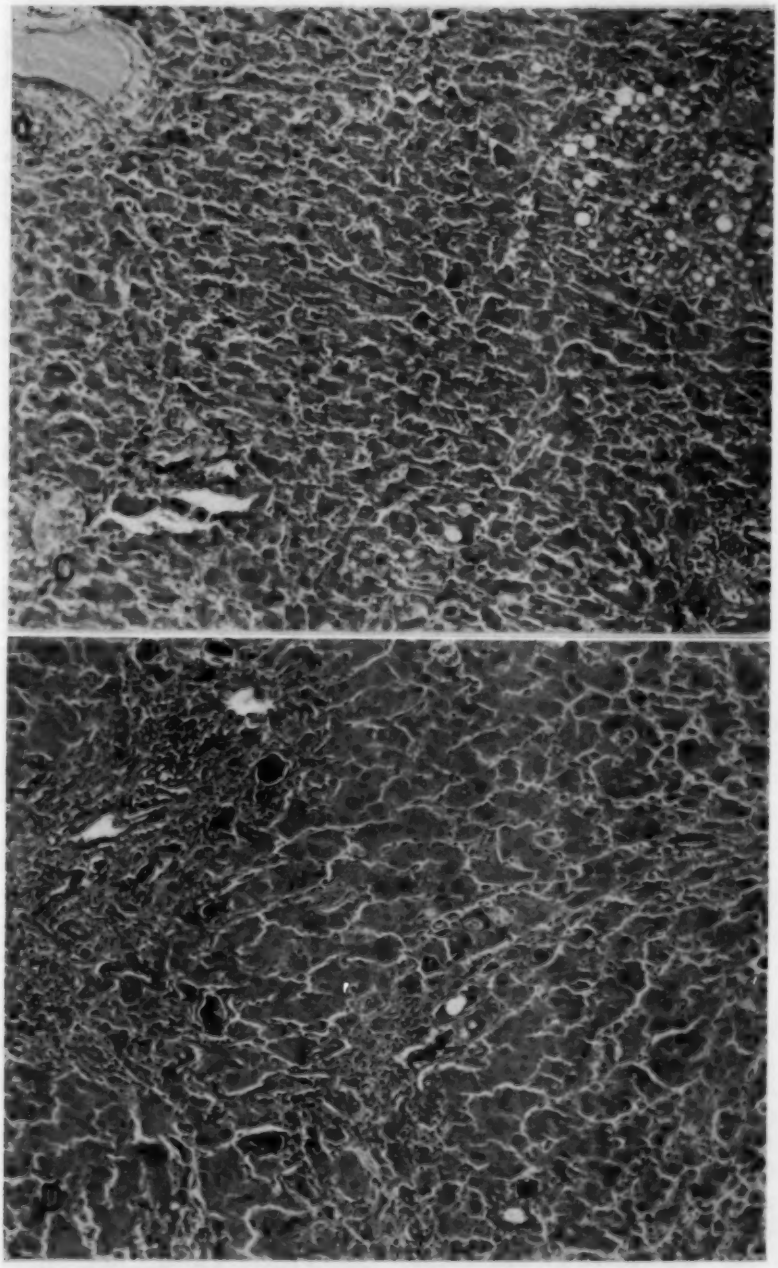


FIG. 2C (*above*). Acute phase of hepatitis: degenerative parenchymal changes, foci of inflammatory cells, and stasis of bile. H & E × 60.
D (*below*). Regenerative phase of acute hepatitis. H & E × 60.

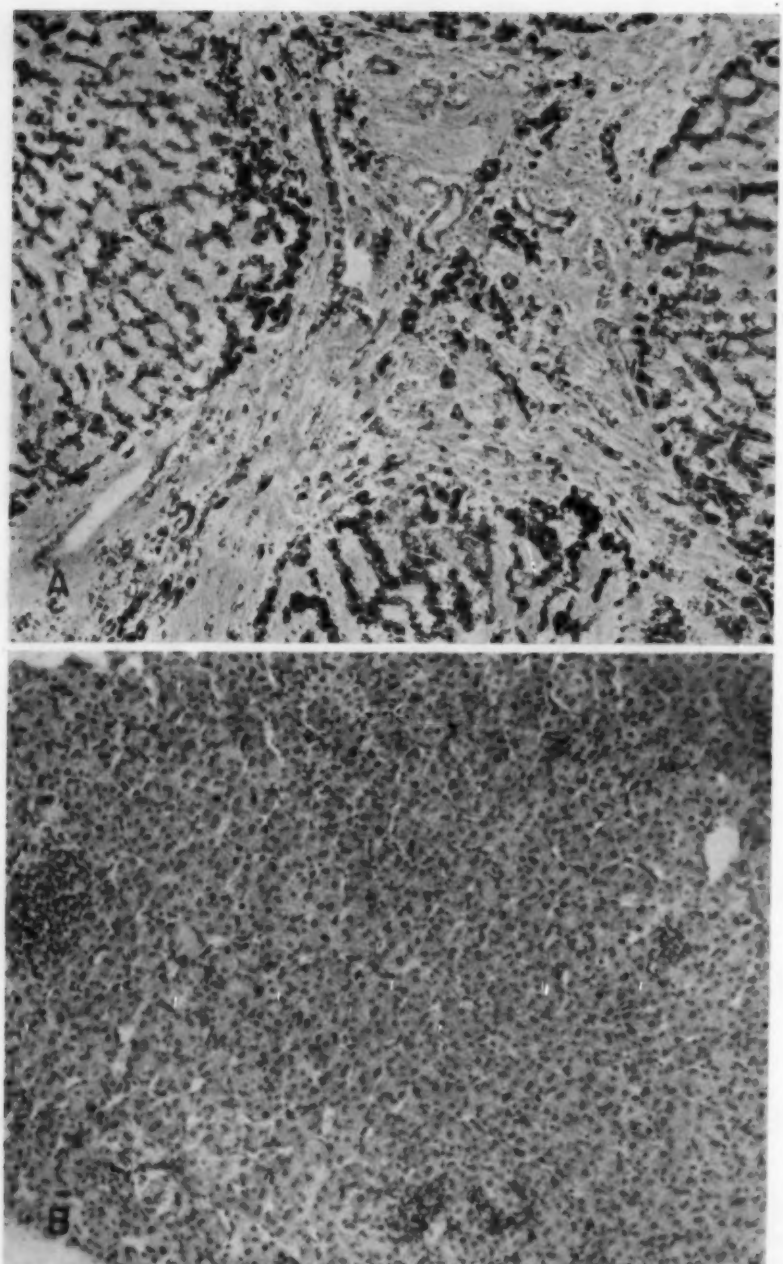


FIG. 3A (*above*). Hemochromatosis: portal cirrhosis and deposits of hemosiderin in stroma, hepatic cells, Kupffer's cells and epithelium of bile ducts. Berlin Blue × 60.
B (*below*). Granulomatous hepatitis. H & E × 60.

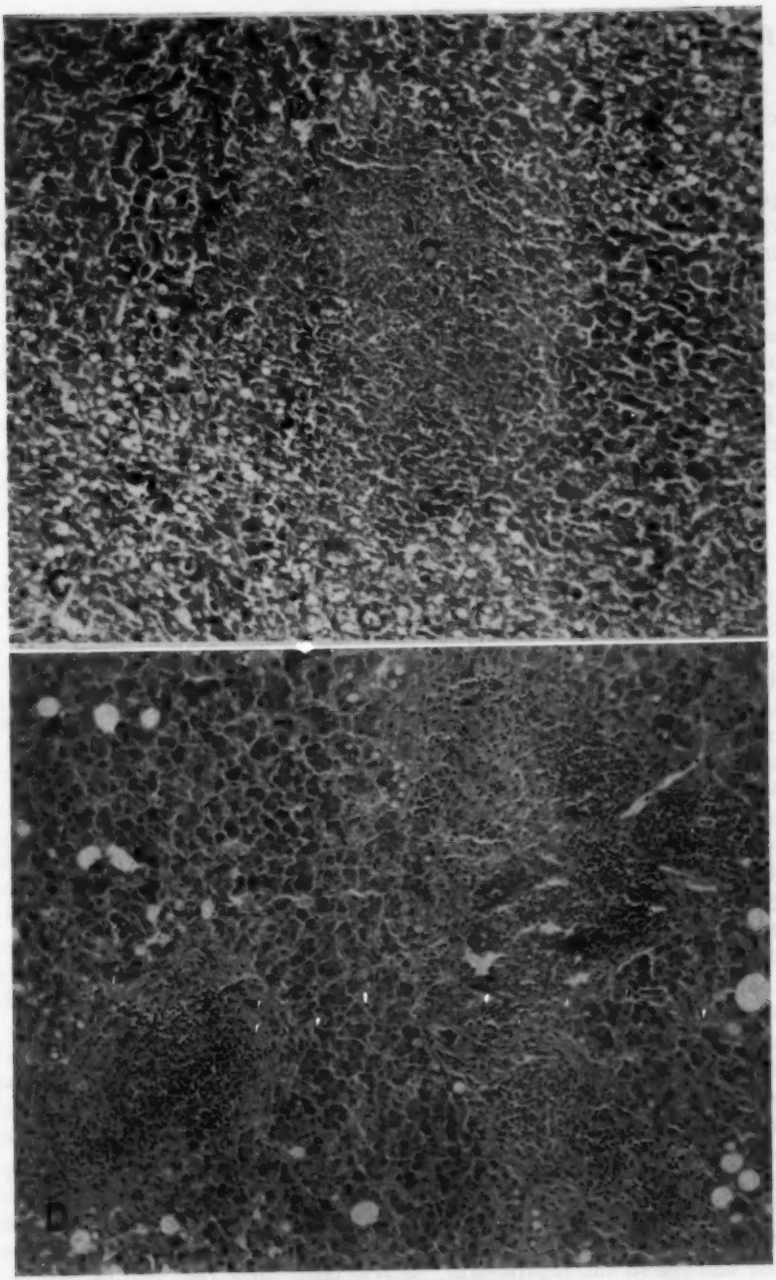


FIG. 3C (*above*). Miliary tuberculosis of liver. H & E × 60.
D (*below*). Lymphosarcoma of liver. H & E × 60.

8. *Banti's Syndrome:* There was one case which fulfilled the diagnostic criteria of Banti's syndrome. Histologic examination of the hepatic biopsy revealed nonfatty portal cirrhosis.

9. *Sarcoidosis:* Uveoparotid fever and cervical and axillary lymphadenopathy were salient physical findings in one case of sarcoidosis. Noncaseating miliary granuloma and normal hepatic cells were demonstrated histologically in the biopsy of the liver (figure 3B).

10. *Miscellaneous:* There were eight cases in which needle biopsy of the liver was performed in an attempt to identify or confirm a systemic disease. Histologic examination of these biopsies revealed hemosiderosis in a case of idiopathic hemolytic anemia, two cases of lymphosarcoma (figure 3C), one of giant follicular lymphoma and three of granulomatous hepatitis. The clinical diagnosis was never conclusively established in the latter three cases. Miliary tuberculosis of the liver was demonstrated by biopsy of the liver in one case and confirmed by culture of the hepatic tissue (figure 3D).

Discussion

Diagnostic Indications for Needle Biopsy of the Liver: An enlarged liver of undetermined cause is an indication for needle biopsy of the liver.[12] Subclinical hemochromatosis,[13] latent portal cirrhosis, amyloidosis,[14-15] hepatoma, cholangioma, lymphoma, leukemia, von Gierke's disease, polycystic disease of the liver,[16] Gaucher's disease and fatty infiltration of the liver [17] are some obscure pathologic conditions that produce an enlarged liver. The transition of a fat-infiltrated liver to a fatty cirrhosis in experimental animals and in man has been a subject of study by many investigators.[18] The pathologic course of a fatty liver can be followed adequately by needle biopsy technic. The histologic picture of nodular regeneration, fibrosis and hepatic cellular injury in a needle specimen of the liver unquestionably establishes the pathologic diagnosis of portal cirrhosis. Fatty infiltration in the regenerative nodules of portal cirrhosis is found commonly when chemical hepatotoxins, alcoholism, diabetes or dietary deficiency is a pathogenic factor.

Metastatic neoplasms of the liver are identified in approximately 80 to 90 per cent of established cases. Direct biopsy of a local metastatic nodule of the liver proves a valuable diagnostic measure. When malignant neoplasm of the liver is suspected, histologic examination of a fresh-frozen section of the hepatic specimen affords immediate diagnostic evidence. The three cases of hepatic melanoepithelioma represented the quasi "glass-eye-hepatomegaly syndrome," i.e., antecedent ocular enucleation for a malignant melanoma of the choroid and an enlarged metastatic liver.

Needle biopsy of the liver is a reliable procedure for diagnosing and following the course and various sequelae of acute hepatitis. In general, diffuse damage to the hepatic cells, balloon cells, early regenerative hepatic

cells, scattered foci of lymphocytes, proliferation of Kupffer's cells, and often stasis of bile characterize histologically the liver of acute viral hepatitis.[19-21] Extensive and diffuse necrosis of the liver with complete loss of hepatic architecture is demonstrated in acute fulminant hepatitis.[22] Certain post-hepatitic sequelae such as fatigue and gastrointestinal symptoms, persistently abnormal hepatic function tests, jaundice, relapse of hepatitis, cirrhosis, hepatomegaly or splenomegaly should be studied by needle biopsy of the liver to determine the presence or type of residual hepatic injury.[23-28]

The only reliable diagnostic technic to confirm the diagnosis of hemochromatosis is needle biopsy of the liver, particularly if the disease is subclinical.[29-30] Quantitative estimation of iron in the needle biopsy specimen of the liver in cases of hemochromatosis always reveals an abundance of this metal. A hyperchromic, macrocytic anemia or aplastic anemia is found infrequently in cases of hemochromatosis. When multiple transfusions of blood are administered therapeutically in any case of chronic anemia, hemosiderosis of the liver rather than hemochromatosis may be demonstrated histologically in the hepatic specimen.[31]

Limitations of Needle Biopsy of the Liver: It is inadvisable to perform a needle biopsy of the liver in the presence of conditions which increase the risk of postbiopsy hemorrhage, exemplified by abnormal prothrombin, bleeding or clotting times, thrombocytopenia or diffuse hemangiomata of the liver.[32, 33] Aggravation of pulmonary infection, pleural effusion and pneumothorax by the passage of a needle transthoracically may induce the spread of infection or lead to intrathoracic hemorrhage. An abdominal paracentesis should be performed to relieve ascites prior to performing a needle biopsy of the liver. An unsatisfactory specimen or a right hydrothorax results from needle biopsy of the liver in the presence of ascites. Bile peritonitis is another complication of needle biopsy observed most often in cases of obstructive jaundice. Intrabiliary pressure is elevated in these cases, and perforation of the liver capsule by a needle facilitates leakage of bile into the peritoneal cavity. Multiple needle biopsy punches in cases of obstructive jaundice are hazardous procedures. The presence of a subdiaphragmatic abscess, hepatic abscess or peritonitis should contraindicate a needle biopsy of the liver.

Postbiopsy pain which required some analgesic medication was present in 34 out of 144 cases. It commonly followed the intercostal technic and persisted usually for a few hours. The usual sites of pain are the biopsy area and the right supraclavicular space, the latter being the result of diaphragmatic irritation. Splinting may occur at the site of the biopsy. Either insufficient local anesthesia of the skin, fascia, intercostal muscles, diaphragm, peritoneum and Glisson's capsule with 1 per cent procaine, or trauma due to multiple biopsies, may induce postbiopsy pain. The use of intravenous tetraethylammonium chloride has been advocated as an analgesic measure, but this procedure is of questionable value.[34] The parenteral administration

of codeine or Demerol usually suffices. Transient anxiety may coincide with postbiopsy pain.

A phenomenon designated "pleural shock" developed in eight cases following the intercostal approach. This was characterized by hypotension, perspiration, absence of tachycardia, and pain in the region of the biopsy persisting for one to two hours. Bile peritonitis [35, 36] complicated two cases of obstructive jaundice, one of which was fatal. Necropsy disclosed cholelithiasis, biliary calculi in the intrahepatic and common bile ducts, hydrohepatosis and focal hepatic necrosis. Surgical drainage of multiloculated pockets of bile was necessitated in the second case of bile peritonitis. Intrapleural or intra-abdominal hemorrhage following needle biopsy of the liver was not an obvious complication in this series. A small pneumothorax developed in one case employing the intercostal technic, and a right hydrothorax occurred in another case which had moderate ascites. Apparently, ascitic fluid seeped through a perforated diaphragm. Penetration of the gall-bladder [37] or the colon, and biopsy of the right kidney [38] are further complications of needle biopsy.

Needle biopsy of the liver may lead to an incorrect clinical diagnosis. There were two cases of established metastatic adenocarcinoma of the liver unconfirmed by a needle specimen. Instead, histologic examination of the needle biopsies revealed normal hepatic tissue. On the other hand, this technic may rectify an incorrect clinical diagnosis. Clinical features in one case suggested unequivocal primary biliary cirrhosis with xanthomatosis, but histologic examination of the biopsy of the liver disclosed metastatic pancreatic adenocarcinoma. Biopsy of the liver disclosed hemochromatosis in two cases in which the diagnosis of portal cirrhosis was originally presumed. These cases are examples of subclinical or asymptomatic hemochromatosis. Histologic examination of a biopsy in two cases of unexplained enlarged livers demonstrated portal cirrhosis. A hepatoma and portal cirrhosis, respectively, were demonstrable histologically in two cases of indeterminate hepatomegaly.

The pathologist is frequently unable to differentiate between chronic hepatitis with jaundice [39] and obstructive jaundice.[40-41] Initially, hepatic specimens from patients with primary biliary cirrhosis are characterized histologically by the presence of an extensive chronic pericholangitis, often with stasis of bile and the appearance of normal hepatic cells. It is at this stage that the term "cholangiolitic hepatitis" may be employed correctly.[42] A prolonged regurgitation type of jaundice, observed especially in women and associated with pruritus, hepatomegaly, splenomegaly, xanthomatosis, cutaneous melanosis and relatively normal hepatocellular function tests, is a clinical feature in these cases. The transition from cholangiolitic hepatitis to cirrhosis occurs later in the course of this disease.[43-46] The liver of primary biliary or cholangiolitic cirrhosis may be pathologically indistinguishable from portal or even postnecrotic cirrhosis. Portal hypertension

and hepatic insufficiency are clinical features of the terminal stage of primary biliary cirrhosis. There are no characteristic histologic features which differentiate biliary cirrhosis from "xanthomatous biliary cirrhosis." The histologic differentiation between primary and secondary biliary cirrhosis is unreliable.

Histologically, hepatic specimens from cases of extrahepatic obstructive jaundice without cirrhosis disclose stasis of bile radiating like spokes in a wheel in the hepatic lobule and minimal parenchymal damage.[47] In postnecrotic cirrhosis the regenerative nodules are too large to be adequately demonstrated in the specimen obtainable by needle biopsy.[48-51] Therefore, information derived from clinical findings, together with histologic evidence of diffuse hepatitis and stromal proliferation in the liver, is suggestive of postnecrotic cirrhosis. Whether valid cardiac cirrhosis exists is dubious. Instead, hepatic fibrosis, passive congestion and centrilobular necrosis are hepatic histologic features observed in cases of congestive heart failure.[52]

Granulomatous hepatitis or miliary granuloma of the liver may be observed histologically in cases with established sarcoidosis,[53-55] brucellosis,[56] histoplasmosis,[70] syphilis, tularemia and lymphoma, and therefore is a nonspecific histologic finding. Sufficient hepatic tissue may be aspirated through the Terry needle, however, to diagnose sarcoidosis both macroscopically and histologically.[57] The small caliber of liver tissue procurable by a needle is usually insufficient for culture.[58]

It is apparent that needle biopsy as a blind procedure may fail to identify such focal hepatic lesions as a metastatic neoplasm,[59] focal cirrhosis,[60] parasites, hamartoma or cysts. Serial histologic sections of hepatic needle biopsies increase the chance of identifying these focal conditions. On the other hand, there is a high degree of diagnostic correlation when needle and necropsy specimens of diffuse pathologic processes of livers are compared.[61] Wedge biopsies of the liver obtainable during an abdominal operation afford the pathologist a larger specimen.[62] The lack of correlation of hepatic histologic changes with certain clinical and biochemical data in cases of liver disease has been postulated.[63-70]

Summary

1. The diagnostic indications of needle biopsy of the liver are indeterminate hepatomegaly, portal cirrhosis, hemochromatosis, primary and metastatic neoplasms, hepatitis or its various sequelae, and polycystic disease of the liver.

2. Certain diagnostic limitations of this procedure include random biopsies of focal pathologic processes of the liver, postnecrotic cirrhosis, and the differentiation of primary from secondary biliary cirrhosis. The histologic differentiation of obstructive jaundice from chronic parenchymatous jaundice is not absolute. The syndrome of primary biliary cirrhosis is characterized histologically in an early stage by chronic pericholangitis, often

with stasis of bile (cholangiolitic hepatitis) and, at a later stage, by a cirrhosis indistinguishable from either portal or postnecrotic cirrhosis.

3. Granulomatous hepatitis or miliary granuloma of the liver is a nonspecific histologic diagnosis.

4. The only reliable method for diagnosing hemochromatosis is needle biopsy of the liver.

5. The small quantity of the hepatic biopsy material makes the culture of the tissue for bacteria and fungi difficult.

6. Contraindications to needle biopsy of the liver include hemorrhagic tendencies, diseases of the right lower lung, diaphragm and peritoneum, ascites, and multiple biopsy punches in cases of obstructive jaundice.

7. Complications of needle biopsy of the liver are pain, "pleural shock," hemorrhage, pneumothorax, hydrothorax, bile peritonitis, perforation or penetration of an adjacent organ, and death.

8. Needle biopsy of the liver is a valuable diagnostic measure complementing the history, physical findings and biochemical tests in cases of hepatic disease.

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SCHISTOSOMA MANSONI: A STUDY OF 26 PUERTO RICANS IN A NON-ENDEMIC AREA *

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Introduction and General Remarks

The presence of Puerto Rican troops of the U. S. Army in the European Theater presented the opportunity of studying *Schistosoma mansoni* in a non-endemic area.

These troops passed the usual induction physical examination and were considered to be in good health. Only one patient in this series of 26 was admitted to the hospital with the diagnosis of schistosomiasis; the remaining 25 were admitted with such complaints as frostbite, fracture, and some medical conditions usually not related to schistosomal infestation. Opportunity was afforded to study Puerto Rican troops admitted to the hospital, and a surprising number were found to have chronic schistosomiasis. In all of these cases the infestation had been acquired from two to 14 years previously, possibly even earlier.

The diagnosis was made by the finding of ova in a stool examination or by demonstrating their presence in rectal biopsy tissue. In the early stages of this study these tests were done sometimes for clinical indication, but the majority of the examinations were requested after it became evident that schistosomiasis, if searched for, could be found with fairly high frequency. It should be noted that these young men had met certain physical qualifications and that they had completed the rigors of basic training. They did not present the picture of a severe chronic illness. They were mildly, chronically ill, and the interpretation of this condition was complicated by the frequency with which other parasites were found in the course of routine stool examinations.[1] Our patients presented a mild form of organ involvement. The obviously ill Puerto Ricans were undoubtedly weeded out prior to entering the Army or during basic training; the apparently healthy individuals remained.

Epidemiology and Pathogenesis

These topics have been well covered in several excellent works in the literature.[2, 3, 4, 5, 6] The following remarks are therefore confined to features which apply to our patients, who show the effects of the disease in a non-

* Received for publication August 10, 1953.

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endemic area. All of these men were from Puerto Rico, mainly from towns and villages where the disease is widespread, and where the snail *Australorbis glabratus* is well established in the streams, rivers and irrigation ditches.[5] Some of these patients, however, had left Puerto Rico years before they entered the United States military service and had settled in other non-endemic areas, such as New York City. Our study of these patients indicates that the majority have chronic mild symptoms of the disease. The fact that they are passing live or dead ova in the stool and showed live or dead ova in their rectal biopsies indicates that, although some of the patients had been treated for schistosomal infestation while in Puerto Rico, they had either failed to respond to treatment or had been reinfested by the parasite. Apparently the disease in the untreated remained in a relatively quiescent state.

The following must be remembered concerning epidemiology:

1. Man is the definitive host and reservoir, while certain species of snails are the intermediate host.
2. Sluggish or still water in a tropical or subtropical climate and the presence of the appropriate snail are essential for the propagation of the parasite in the extra-human portion of its life cycle.
3. The adult worms are found mainly in the tributaries of the portal vein of man and can survive there to produce ova for many years. This is well illustrated in the paper by Wallenstein,[7] which reports that live worms were found (at autopsy) in the human host 26 years after the last possible infection.
4. The adult female worm lays her eggs in the small tributaries of the portal vein. These lateral spined ova can penetrate the wall of the small venules. Some migrate through the lower bowel mucosa to enter the lumen, while others in the venules of the bowel wall may be swept back into the venous return to the liver. The veins most frequently affected are the superior hemorrhoidals.
5. The egg, on being discharged into the feces, must reach water, and there it hatches out a free swimming miracidium which must find the appropriate snail in which to mature. Since this intermediate host does not exist in Germany, this group of patients could neither transmit nor acquire the infestation there. This also presented an ideal situation for evaluation of the effects of therapy.

The parasites, as far as we could determine, were confined to the colon and liver in our cases. Manifestations elsewhere were unusual. One of our cases showed urinary bladder involvement in the form of bullae, vesicles and minute hemorrhagic papillae. This patient had symptoms of schistosomiasis and showed involvement of the rectal mucosa.

The microscopic lesions noted in the biopsied rectal tissue ranged from eosinophilic and mononuclear infiltrates surrounding well preserved ova to fibrotic nodules with no evidence of the remains of ova. They were found

in and out of the venules of the mucosa and submucosa. Fresh granulomata with giant cells occupying the shells of ova were very frequently observed (figure 1).

Liver tissue obtained by biopsy showed various stages of involvement, ranging from acute schistosomal hepatitis to advanced cirrhosis. Ova were present in the nature of calcified forms, forms surrounded or partially engulfed by giant cells, and apparently viable forms with minimal reaction.

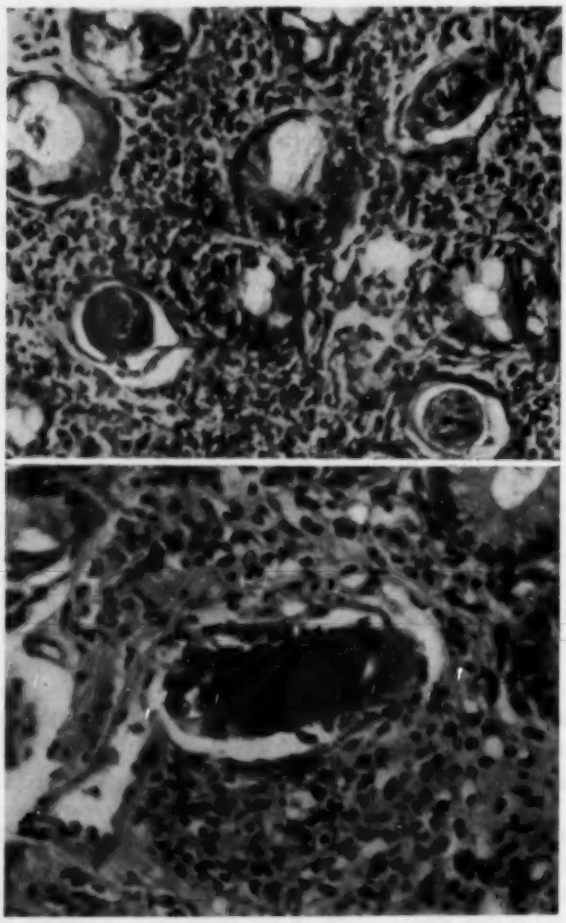


FIG. 1. Rectal biopsies. (a) (*above*) Ova in mucosa at 1, 5 and 7 o'clock. Note surrounding reaction and spines of ova. H & E × 200. (b) (*below*) Ova in submucosal venule. H & E × 250.

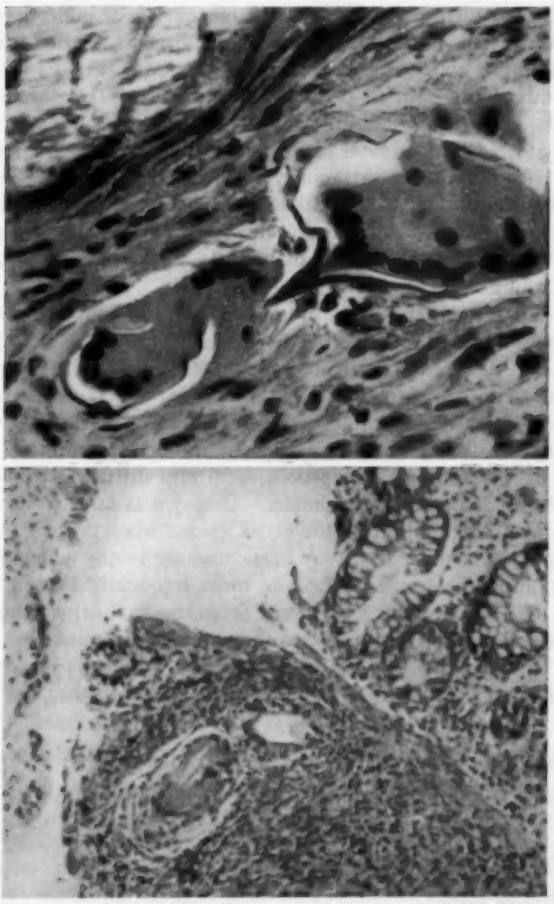


FIG. 1. Rectal biopsies. (c) (*above*) Giant cells occupying the ova in the mucosa. H & E × 380. (d) (*below*) Granulomata of submucosa showing varying degrees of fibrosis. H & E × 150.

The portal triads were most prominently involved, although in some of the sections the ova were found in various portions of lobules with and without accompanying cellular infiltration.

CLINICAL POINTS

Schistosomal involvement could be suspected in most of these patients following a careful system review. The fact that they had been raised in certain areas in Puerto Rico indicated the need of a careful search. The

majority of these men appeared to be undernourished, underdeveloped and mildly chronically ill. Their main complaint, difficult to elicit initially, was epigastric pain. This pain was brought on or aggravated by eating, and closely resembled the pain of peptic ulcer except for the absence of point localization. Diarrhea, though frequent, was not nearly so frequent as epigastric pain. Bloody stools were found in several patients. Shortly after this series was begun, sigmoidoscopy and rectal biopsy became part of a routine examination of Puerto Rican troops admitted to the Medical Service. However, because of the number of patients, the tests could not be done on everyone. We believe that time was the only limiting factor in discovering additional cases.

Even when the patients who presented positive stool examinations did not have symptoms, sigmoidoscopy with few exceptions revealed certain abnormalities. These were: friability of the bowel wall, congestion and edema of the mucosa (sometimes accompanied by punctate submucosal hemorrhages), and in several cases the characteristic finely granular appearance of the bowel wall.[8, 9] This granular appearance, sometimes referred to as "cobblestone," was both focal and diffuse. Biopsy of these areas revealed ova and/or granulomata. Biopsy was taken routinely during sigmoidoscopy and directly from the gross lesions when present. No ulcerations or papillomata were seen. A bronchoscopy biopsy pinch forceps was used in obtaining the tissue. The site most frequently chosen was at the level of the first rectal valve, 8 to 10 cm. from the anal orifice; however, one or more specimens were taken from other areas concomitantly. This area is drained by the superior hemorrhoidal veins. The biopsy specimen was preserved in formaldehyde and examined, as will be further described.

Laboratory Aids in Diagnosis and Evaluation of Treatment

In addition to the history and physical examination, the following procedures were used in the study of these patients:

1. Stool examination.
2. Rectal biopsy.
3. Liver function tests.
4. Complete blood counts.
5. Urinalyses.
6. Chest x-rays.
7. Liver biopsy.

The main principle in the examination of stools is that the identification of one ovum is considered evidence for the existence of the disease. Treatment was considered warranted only if the ova were demonstrated to be viable. Another principle followed in the examination of stools was that repeated negative stools coinciding with negative rectal biopsy were necessary before we concluded that the patient did not have chronic schistosomiasis. The cyclic nature of the appearance of ova in the stool is well known.[2] Well formed or firm stools were preferred for examination, be-

TABLE I

Comparison of Rectal Biopsy and Stool Examination in 26 Cases of *Schistosoma mansoni*

Case No.	Biopsy Finding	Stool Examinations								
		1st	2nd	3rd	4th	5th	6th	7th	8th	9th
1	+	−	−	−	−	−	−	−	−	+
2	+	+								
3	+	−	−	+						
4	−*	−	+							
5	+	+								
6	+	−	−	−	−	−				
7	+									
8	−**	−	−	−						
9	+	+								
10	+	+								
11	+	−	−							
12	+	+								
13	+	−	+							
14	+	−								
15	+	−	−	−						
16	+	−	−	−						
17	+	+								
18	+	−	+							
19	+	−	−	+						
20	−	−	−	−	−	+				
21	+a*	−	−	−	−					
22	+	+								
23	+	+								
24	+	−	+							
25	+	+								
26	+	−	+							

* Gross bowel changes on sigmoidoscopy.

** Diagnosis proved by rectal biopsy elsewhere.

a First biopsy was negative but because of marked bowel changes a second biopsy was done which was positive.

cause this type of stool serves to scrape possible ova-containing blood, mucus and debris from the superficial portion of the bowel mucosa as the stool proceeds down the lumen. Blood and mucus accompanying the stools were found to be excellent sources for ova, and were therefore carefully searched when obtained.

The reliability of the rectal biopsy in helping to establish the diagnosis is shown in table 1. Specimens taken from areas of punctate hemorrhage or from "cobblestone" areas showed ova or the results of their having been present (granulomata). In a few cases rectal biopsy was positive when no abnormalities were seen in sigmoidoscopy. We preferred the paraffin section method for examination of the biopsy specimen. It allowed the greatest accuracy in the evaluation of the specimen, since serial sections could be done. It also gave a permanent record, and it revealed the presence of schistosomal granulomata. The finding of granulomata only, however, was not considered to represent an active infestation, and in the case of patients who showed only this, further stool examinations and a repeat rectal biopsy were performed before a decision as to treatment was reached.

Liver function tests were done for three reasons:

1. To attempt to discover hepatic involvement by clinical laboratory methods.
2. To attempt to evaluate possible liver damage following tartar emetic therapy.
3. To attempt to correlate liver biopsy findings with clinical laboratory tests.

Liver function studies (table 2) were done before, during and after treatment. This study revealed that only two patients had 4 plus cephalin flocculation tests prior to treatment. Both had liver biopsies and both showed hepatitis. The first, L. C., had an active schistosomal hepatitis (figure 2). The other, F. V. S., showed numerous granulomata without the presence of ova. A follow-up liver biopsy in each case failed to reveal the previously noted involvement. This is difficult to interpret, and one

TABLE II

Liver Function Studies in 23 Cases of *Schistosoma mansoni* Pre and Post Treatment

	Pre Treatment					Post Treatment				
	BSP	TP	CF	TT	TSB	BSP	TP	CF	TT	TSB
VO	2.5	7.2		4.8		0.8	7.6		4.7	
HM	3.4	7.5		2.0	0.72	5.5	8.1	2+	1.9	
MM	2.5	7.3	0	3.4	0.73	7.0	7.6	1+	4.5	
FPC	3.0	6.0		2.7		2.0		1+	1.0	
TC	1.0	7.4	2+	1.4	0.36	1.5	6.7	1+	2.7	
CR	2.5	7.4	0	2.4	0.56	2.3	6.8	1+	1.7	0.48
SR	4.5	7.5	0	2.0	0.88	4.0	7.3	1+	0.5	
RS	3.7	5.9	3+	1.7		7.5	5.6	2+	1.4	0.32
MJ	2.0	5.7	3+	3.0	0.60	5.5	6.1	1+	2.0	1.30
PRQ	0.5	7.5	0	3.2	0.30	4.3	6.8	0	3.4	0.44
LT	3.5	7.9	1+	2.7	0.30	21.3	7.8	1+	4.5	0.64
PRR	1.5	7.5	3+	3.8	0.24	2.5		4+	4.1	0.36
JH	4.0	7.3	2+		0.96	4.3	7.2	0	1.4	0.64
PSC	4.0	7.5	1+	1.7	0.48	6.7	7.5	0	1.4	
JR	5.0	6.1	3+	5.2	0.84	4.2	6.4	0	6.0	
VMS	3.3	7.5	1+	0.4	0.80	13.5	7.4	0	1.0	
LJR	2.0	7.7	1+	1.4	0.24	4.0	6.3	0	3.4	
OM	2.3	6.9	1+	4.1	0.48	5.5	5.9	0	1.9	
RN	1.0	6.9	0	2.4	0.16	3.5	7.1	0	5.6	
LC	5.0	7.7	4+	2.2	1.20	8.5	6.3	2+	1.7	
TG	1.7	7.6	2+	3.0	0.32	2.5	7.9	4+	5.4	0.45
EOA	3.5	6.9	0	0.5		7.5	7.2	0	2.7	0.45
FVS	2.3	7.4	4+	2.2	1.20					

BSP Bromsulfalein. Dose 5 mg. per kg. of body weight. Test sample drawn at 45 min.
TP Total protein.
CF Cephalin flocculation.
TT Thymol turbidity. TSB Total serum bilirubin.

Tabulation of liver function studies reveals that patients L. C. and F. V. S. show significant pretreatment cephalin flocculation and total serum bilirubin levels. Both showed liver involvement in liver biopsy tissue. These same patients showed no liver tissue involvement post-treatment. Patient L. T. and others who showed abnormal post-treatment function tests showed no liver involvement in liver biopsy tissue.

hesitates to state that the patients were cured by the treatment. It should be noted, however, that the granulomata observed in the initial biopsies showed little or no fibrous proliferation. We believe that such lesions are reversible.

A case of severe schistosomal cirrhosis was discovered at another hospital in this theater by the liver biopsy (figure 2). The complication of

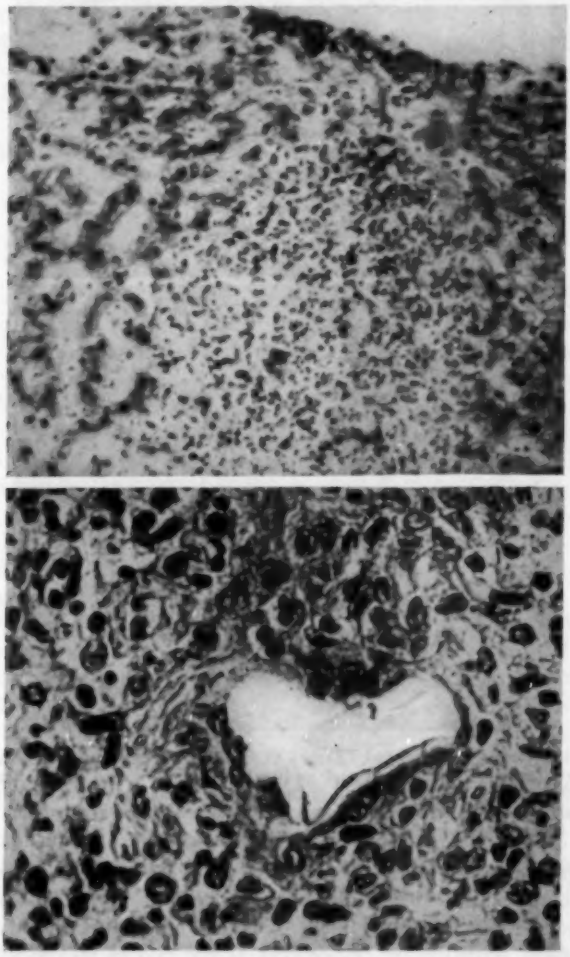


FIG. 2. Liver biopsy tissue. (a) (*above*) L. C. shows one of the many granulomata observed. H & E × 150. (b) (*below*) L. C. partially destroyed ovum in the center of a granuloma. Masson × 380.

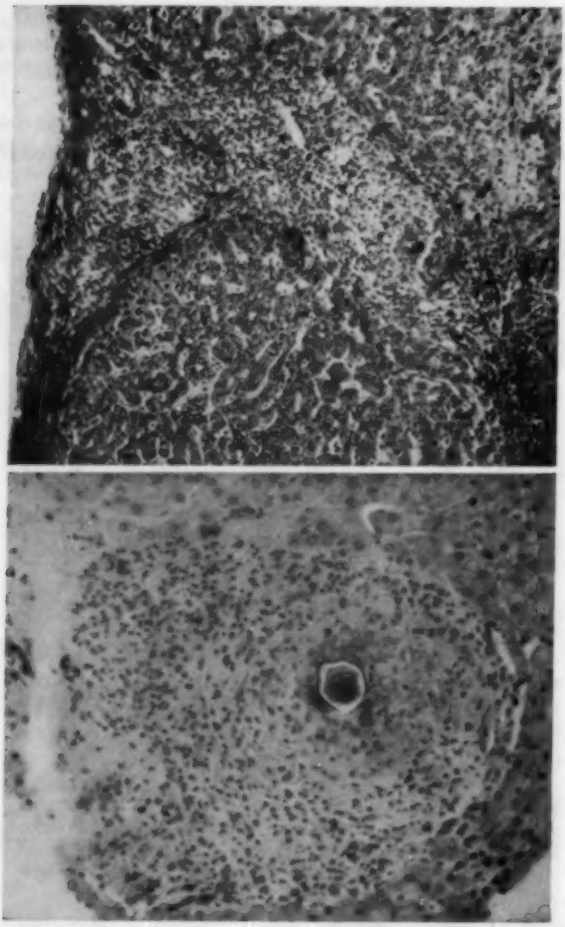


FIG. 2. Liver biopsy tissue. (c) (*above*) C. B. Severe schistosomal cirrhosis. Pseudolobulation, proliferation of bile ducts and infiltration of the widened portal fields are seen. Masson × 100. (d) (*below*) C. B. One of the many granulomata in the same case as (c), showing a sagittal section of an ovum. It is at the edge of a portal triad and extends into the adjacent lobule. Masson × 150.

hepatomegaly during treatment occurred in five patents. Three of these had liver biopsies and all revealed normal liver tissue. The cause of the hepatomegaly remains unexplained. One of these three patients had a bromsulphalein retention of 21 per cent at the end of treatment (L. T.), but the remaining liver function studies were normal.

Anemia was not seen in these patients. This is perhaps unusual, but

these patients had been screened prior to our seeing them. Eosinophilia, while frequent, was not invariably present. Eosinophil counts varied from 1 to 35 per cent, and wide ranges were seen in individual patients. An absolute eosinophilia, associated with leukocytosis, was noted in 20 per cent of our cases during treatment. This will be discussed later.

No significant abnormalities were noted in routine urinalyses except in the one patient who had urinary bladder involvement. He showed an intermittent sterile pyuria.

Chest x-rays showed no abnormalities in this series of patients.

Liver biopsies were performed for investigative purposes on eight of our patients. The technic was that of the transthoracic approach, using the Vim-Silverman needle as modified by Nelson.[10] We feel that the liver biopsy may be a useful adjunct to the rectal biopsy and stool examination if there is clinical indication, but it is not recommended as a routine procedure.

Treatment

Treatment consisted of the intravenous administration of 0.5 per cent tartar emetic.[11] This was limited to a total of 1.6 gm. during the course of 30 days. Complications were frequent, and arm and shoulder pain occurred toward the end of treatment in all patients receiving this drug. In order of frequency, complications were: 1. arthralgias; 2. myalgias; 3. nausea; 4. vomiting, and 5. hepatomegaly.

One patient developed a papular skin rash of the hands which disappeared following treatment. Cough was not frequent, for after treatment of the first several patients the 0.5 per cent tartar emetic dose was diluted in 500 to 1,000 c.c. of normal saline. This eliminated the cough almost entirely. The patients were confined to bed for from one to two hours following completion of the injection, to prevent the so-called "postural ischemia" of the liver.

During treatment a routine urinalysis, electrocardiogram and complete blood count were done every 10 to 14 days. No significant changes were noted in the urines examined. Significant electrocardiographic changes occurred in eight patients, all of whom showed some alteration in the T-waves (flattening to inversion).[12, 13] One tracing revealed a transient, prolonged P-R and QT interval. The percentage of abnormalities in various series depends upon the criteria used for evaluating abnormalities, and also upon the time relationship of the tracing to the injection of tartar emetic. Abnormalities occurring during treatment disappeared within three months following the last injection of the drug.

The most interesting laboratory change which occurred during treatment was an absolute increase in the number of eosinophils. This occurred in 20 per cent of our cases, and was usually seen one to two weeks after the initiation of treatment, at the time when the full dose of tartar emetic

was attained. It was associated with a leukocytosis of 15,000 to 35,000. As seen in the graph (figure 3), this increase bears a definite relationship to the treatment. It is notable that the total percentages are occasionally over 70. This eosinophilia and leukocytosis subsided following treatment and was not associated with any clinical or other laboratory observations or procedures. If the eosinophilia during treatment indicates the liberation of the foreign protein of the destroyed parasite into the host's tissues (as we believe), then the eosinophilia must represent effective treatment. However, one cannot conclude that those patients who did not reveal an increased eosinophilia during treatment did not respond. This latter group, which comprised 80 per cent of the series, may have been either refractory

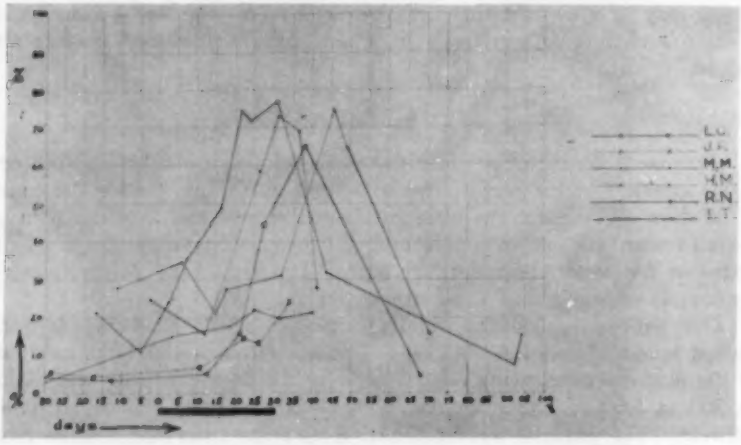


FIG. 3. Eosinophilic response to treatment with tartar emetic. Solid bar under "days" indicates beginning and duration of treatment. Note that the eosinophilic response usually begins one to two weeks after the initiation of treatment, when the full dose of tartar emetic is attained.

to treatment or unable to produce an eosinophilia. The five patients in whom eosinophilia occurred presented the most remarkable symptomatic and clinical improvement of the entire group. Therefore, we believe that the occurrence of this absolute eosinophilia is an indication of the efficiency of treatment.

The clinical change that took place in the majority of our patients was remarkable. Whereas before treatment some of these patients had had no specific complaints, the same patients when seen months later stated that they felt improved generally. They had more energy and an increased appetite. They could eat more, and had lost their former epigastric pain. The majority gained weight following treatment. They appeared much healthier.

Follow-up examinations could not be done in all patients, since some were returned home as a normal military procedure. The only significant finding noted in the immediate post-treatment stool examination was that the stool in all but one case became negative. As it is well known that treatment may inhibit the female from laying eggs for several months without killing her, true evaluation of the effect of treatment could not be made. To ascertain a cure, stool examinations have to be done at least six months post-treatment, and numerous examinations must be made.

None of the patients who were examined on a six month follow-up had a positive rectal biopsy or stool. However, rectal biopsy covers only a minute portion of the total area of possible pathology. It assumes significance only if associated with numerous negative stool examinations and the continued normal appearance of the rectal and sigmoid mucosa. In those who presented an edematous, friable and hemorrhagic bowel wall before treatment, sigmoidoscopy post-treatment revealed disappearance of these lesions. This change was definite. It could lead one to believe that a cure was effected, but, as stated previously, one may only assume that treatment was effective. A long period of follow-up, such as over the course of one year, is necessary before one may reach a conclusion concerning a cure.

Summary and Conclusions

1. An unselected and small proportion of the total Puerto Rican population in the Army in this command was studied. No attempt was made to determine the statistical incidence of infestation with *Schistosoma mansoni*. Judging from the number of cases found in the Puerto Ricans studied in this hospital, the incidence must be high.

2. The presence of the disease should be suspected in all persons who have lived in endemic areas, even if no complaints are elicited.

3. The rectal biopsy paraffin section in this series was found to be the most effective diagnostic tool. Repeated examinations of unpurged stool are important, and were found to be a useful adjunct in diagnosis and evaluation of treatment.

4. The results of liver biopsy compared to liver function tests suggest a correlation between the cephalin flocculation test and the existence of schistosomal involvement of the liver.

5. We believe that absolute eosinophilia during treatment is the first indication of the efficacy of treatment. This point should be further investigated.

6. Further search for a less toxic therapeutic agent is indicated.

Acknowledgment

We are indebted to SFC. Horace Seymour for the time and effort devoted to the photomicrography in this article.

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CASE REPORTS

ENDOCARDITIS DUE TO MICROCOCCUS TETRAGENUS*

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Micrococcus tetragenus (*Gaffkya tetragena*) is an extremely variable bacterium which rarely causes endocarditis. It is closely related to the staphylococcus, and was initially reported (by Gaffky in 1881) to be a saprophytic inhabitant of the respiratory tract. Since that time, *M. tetragenus* has been reported as the infecting organism in approximately 200 patients, with involvement of the respiratory tract, central nervous system, skeletal system, genitourinary tract, and the cardiovascular system. The literature refers to approximately 12 cases of endocarditis due to this organism,[1] only two of which are in the American literature.[2]

The following case illustrates the difficulty of obtaining a cure of endocarditis due to *M. tetragenus* despite massive and prolonged antibiotic therapy.

Case Report

History: This 38 year old white woman became ill in October, 1951, with recurrent aching in the shoulders, ankles and knees. Shortly after the extraction of an abscessed tooth in February, 1952, she developed progressive weight loss, fatigue, shortness of breath and edema of the ankles. The following month an infected laceration of the right forehead was treated with sulfonamides, penicillin and Aureomycin. During April the patient noted irregular fever and a cough, which she ascribed to "bronchitis." Shaking chills, drenching sweats, high fever and paroxysmal nocturnal dyspnea followed. In mid-June she started taking chloramphenicol, 250 mg. four times daily. She became unable to work because of extreme fatigue, shortness of breath, fever, cough, joint pains and edema. With doubling of the dosage of chloramphenicol on June 22 the patient stopped having chills and sweats. Because of complete exhaustion she sought medical aid on June 26 and was hospitalized.

Examination revealed the patient to have a temperature of 101° F., marked dyspnea and orthopnea, slight cyanosis, moderate clubbing of the fingers, two subungual splinter hemorrhages, petechiae of the buccal mucosa, pitting edema of the ankles, distended neck veins, moderate cardiomegaly, a gallop rhythm, a systolic apical thrill accompanied by a loud, coarse, blowing systolic murmur, crepitant râles at the base of the right lung, and moderate enlargement of the liver and spleen. The leukocyte count was 12,300 and the hemoglobin 7.0 gm. per 100 c.c. Gram-positive cocci were isolated from blood cultures. The patient was digitalized on June 27. On the following day the administration of 4 gm. daily of chloramphenicol was begun (figure 1). A mild decrease in fever and improvement in congestive failure resulted, but the

* Received for publication September 8, 1953.
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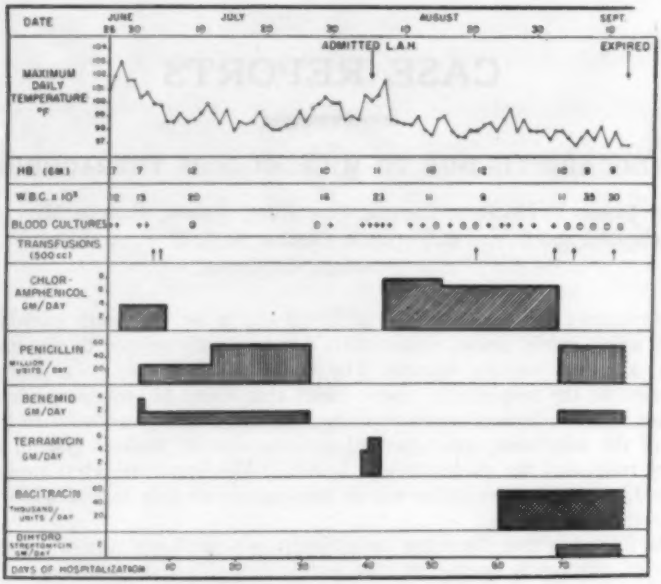


FIG. 1. Clinical course of a case of *Micrococcus tetragenus* endocarditis.

patient continued to appear toxic and complained of severe retrosternal burning pain. In vitro studies showed complete inhibition of the growth of the organism by 10 units of penicillin or 30 mcg. of chloramphenicol per cubic centimeter of broth; partial inhibition by 10 units of bacitracin per cubic centimeter, and no discernible inhibition by 60 mcg. of Aureomycin, 60 mcg. of Terramycin, 10 mcg. of streptomycin, or 1 unit of penicillin per cubic centimeter.

On July 1 the continuous intravenous administration of 30,000,000 units of penicillin daily and the oral administration of 2 gm. of Benemid daily were started. Within three days the patient became afebrile. The chloramphenicol therapy was discontinued on July 5. One week later, immediately following the recurrence of fever, the penicillin dosage was increased to 60,000,000 units daily. The patient again became afebrile on July 17. On July 25 the penicillin therapy was discontinued. Fever promptly recurred and a positive blood culture was obtained. On August 3 the patient developed severe right flank pain, and on the following day Terramycin therapy, in the dosage of 500 mg. every six hours, was started. She was transferred to this hospital on August 5, 1952.

Physical Findings on Admission: Examination revealed an acutely ill, wasted white woman with distended neck veins and clubbing of the fingers. There were no splinter hemorrhages, petechiae or retinal lesions. No dependent edema was present. The temperature was 100° F.; pulse, 120; respirations, 22; blood pressure, 118/77 mm. of Hg. The left border of cardiac dullness was in the midaxillary line. A systolic thrill was present at the apex. Auscultation revealed a presystolic gallop rhythm and a loud, harsh apical systolic murmur. Physical findings in the lungs were normal. The liver was palpable 8 cm. below the right costal margin. The spleen was not palpable. The right costovertebral angle region was markedly tender.

Admission Laboratory Findings: The leukocyte count was 23,200, with 84 per cent neutrophils, 15 per cent lymphocytes, and 1 per cent basophils; the hemoglobin was 10.7 gm. per 100 c.c. Catheterized urine was sterile and contained rare white blood cells. The roentgenogram of the chest showed marked generalized enlargement of the heart with normal lung fields. The electrocardiogram showed right axis deviation and was abnormal due to nonspecific ST segment and T wave changes in Leads II, III, aVF, V_5 and V_6. The blood urea nitrogen was 18 mg. per 100 c.c. Two blood cultures were positive for gram-positive cocci morphologically and culturally identical with the organisms previously recovered.

The organism was beta hemolytic on blood agar and grew moderately on mannitol salt agar without chromogenesis. Catalase and coagulase tests were positive. It produced acid in lactose, dextrose, sucrose, and glycerol broths and in bromcreosol purple milk. It did not form indole or produce nitrates from nitrites. There was no growth in ammonium phosphate media and no liquefaction of gelatin. The bacteria were lethal for mice 12 hours after inoculation. After passage through mice, the organisms formed capsules and were arranged in pairs and tetrads. The cocci were therefore identified as *M. tetragenus.** [3] The cultured organism was resistant to 60 mcg. of Aureomycin, Terramycin or polymyxin, and 20 mcg. of streptomycin, neomycin or sulfadiazine per cubic centimeter of broth. It was inhibited by 1.5 units of penicillin, 1.25 units of bacitracin, or 0.62 mcg. of chloramphenicol per cubic centimeter.

Course in the Hospital: The patient was continued on a low sodium diet, maintenance dosage of digitoxin, and injections of mercurial diuretics. Terramycin was administered in increased dosage until August 7, at which time initial sensitivity studies were completed. The patient was then started on 8 gm. of chloramphenicol daily in divided doses. The oral temperature remained below 99° F. The blood cultures continued to be positive, although progressively longer times were required for visible growth. On August 16 numerous white, shiny patches appeared on the patient's buccal mucosa, tongue and gums. Fungi could not be cultured from the lesions, but they cleared promptly with local gentian violet therapy.

In vitro studies showed no change in sensitivity of the *M. tetragenus* to single antibiotics. Mixed antibiotic studies showed that growth of the organism was inhibited by the combination of 0.07 mcg. of chloramphenicol and 0.62 unit of bacitracin per cubic centimeter of broth, as well as by 0.4 unit of penicillin plus 0.15 unit of bacitracin per cubic centimeter. Treatment with 15,000 units of bacitracin intramuscularly every six hours was added on August 25. Hepatomegaly, anemia, severe anorexia and occasional vomiting continued. The blood cultures of August 28 and 30 showed prompt growth, although the organism obtained on August 30 was still inhibited in vitro by the same concentrations of chloramphenicol, bacitracin or penicillin, alone or in combinations.

On September 3 the chloramphenicol therapy was terminated. The administration of bacitracin was continued, with the addition of 60,000,000 units of penicillin and 1 gm. of dihydrostreptomycin given intravenously and 2 gm. of Benemid orally daily. The patient appeared to improve until September 10, when she became apprehensive and complained of a dull aching pain in the right anterior chest. Examination revealed profuse sweating, cyanosis, a weak, rapid pulse, and blood pressure of 80/60 mm. of Hg. The electrocardiogram showed further right axis deviation. The chest roentgenogram and the blood chemistry findings were unchanged. The last five blood cultures obtained were sterile, but the patient died on September 13, 1952.

Autopsy: The heart was enlarged, weighing 470 gm. A blood culture from the right atrium was sterile. Several vegetations up to 3 mm. in diameter were attached to the edge of the mitral leaflets. The other valves were normal. The coronary

* Sixth Army Laboratory, Fort Baker, California.



FIG. 2. Microscopic section of mitral valve. Innumerable gram-positive cocci are seen. (× 900.)

arteries were patent. On microscopic examination, numerous colonies of cocci were seen in both leaflets of the mitral valve (figure 2). These colonies were surrounded by areas of fibrosis, necrosis, hyaline degeneration with occasional calcification, and scant polymorphonuclear and lymphocytic infiltrations. A few scattered lymphocytic infiltrates were present in the epicardium and myocardium. No evidence of recent or past rheumatic carditis could be found.

The lungs were congested and there was partial atelectasis of the lower lobe of the right lung. There was no evidence of pulmonary infarction. The spleen and right kidney contained several subacute infarctions.

COMMENT

Approximately one-half of the reported infections due to *M. tetragenus* are fatal, although some patients with septicemia or meningitis survived even in the pre-antibiotic era.[1a, 4] Cures have been reported following the use of sulfonamides in *M. tetragenus* meningitis [5] and following the use of Aureomycin in *M. tetragenus* septicemia.[6]

Three case reports are available on the results of treatment of *M. tetragenus* endocarditis with antibiotics. The strain recovered by Barreda [1b] was sensitive to 0.016 unit of penicillin per cubic centimeter of broth despite the fact that the patient had previously been treated with penicillin. The patient recovered following treatment with 40,000 units of penicillin intramuscularly every three hours for 29 days. The organism recovered from Boynton's fatal case [2b] was

initially resistant to the sulfonamides and rapidly developed resistance to penicillin and streptomycin. De Oya and Segovia [1c] reported a case of *M. tetragenus* endocarditis in which the organism was inhibited by 0.078 unit of penicillin per cubic centimeter of broth or 6.25 mcg. of Terramycin per cubic centimeter of broth. Their patient died despite the intramuscular administration of 1,200,000 units of penicillin daily and brief therapy with 2 gm. of Terramycin daily.

In our patient, the cultured organism was resistant to sulfadiazine, Aureomycin, Terramycin, streptomycin, neomycin and polymyxin when first tested. Active endocarditis persisted while the patient was being treated with 30,000,000 units of penicillin and 2 gm. of Benemid daily, and later while she was receiving 7 to 8 gm. of chloramphenicol daily, although the organism remained moderately sensitive in vitro to both penicillin and chloramphenicol. The latter drug was used because of the bacteriostatic effect of small doses in the test tube and its previous successful use in occasional cases of staphylococcic endocarditis.[7] During combined treatment with large doses of penicillin, streptomycin and bacitracin, the blood cultures became sterile but the patient continued to decline and the organisms were still seen in the mitral valve at autopsy.

The ease of development of morphologic variants of the *M. tetragenus* may be related to its frequent resistance to antibiotics. Reimann [8] identified 16 morphologically different strains of *M. tetragenus* after prolonged culture, with smooth, mucoid or rough colonies colored white, yellow, pink, pink-yellow or brown, in addition to a translucent strain and a bacillary strain. These variations were not noted in the organism repeatedly isolated from our patient. Reimann tried without success to hasten the development of strains resistant to heat, cold and hypertonic saline by exposure of the organism to these noxious factors. Mock and Wynne [9] rapidly developed strains of *M. tetragenus* resistant to streptomycin. They observed a two thousand to four thousand fold increase in resistance to streptomycin in five of six strains tested, with two to five passages of the organism through a streptomycin-containing medium. A fortyfold increase in resistance was observed in the sixth strain with five serial passages. They were unable to secure penicillin resistant strains using the same method, and did not report using other antibiotics.

From the few cases reported it would appear that once the *M. tetragenus* becomes entrenched on a heart valve, its eradication is difficult even though the strain recovered may be sensitive to antibiotics in the test tube. In vitro sensitivity studies, however, may provide aid in the intelligent choice of antibiotics to be used.

SUMMARY

Bacterial endocarditis due to *M. tetragenus* is of rare occurrence. Few data are available in the literature on the results of antibiotic therapy in such cases. The patient reported died despite antibiotic therapy in dosages which, according to the sensitivity tests performed, usually prove adequate in curing endocarditis due to other organisms.

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A CASE OF SECRETING PARAGANGLIOMA OF THE ORGAN OF ZUCKERKANDL*

By C. W. Fullerton, M.D., F.A.C.P., J. Carl Sutton, M.D., and I. G. Milne, M.D., *Montreal, Canada*

In recent years increasing interest has been shown in tumors of the pheochromocytoma group, and to date over 300 cases have been reported in the literature. Because of the dramatic clinical picture which these tumors may present, we believe that a high percentage of such cases is reported, and that this has led to an erroneous impression that these are relatively common tumors. In the records of the Teaching Hospitals at McGill University only four of these tumors have been found over a 30 year period, and in three of these cases they were unexpected autopsy findings.

In the majority of cases reported the tumors arose from the chromaffin tissue in the adrenal medulla for which the term pheochromocytoma has been reserved, while the term paraganglioma is used for chromaffin tumors of extra-adrenal

* Received for publication September 16, 1953.
From the Departments of Medicine and Surgery of The Montreal General Hospital.

origin. The principal sites where paragangliomas may occur are in the carotid bodies and the organs of Zuckerkandl, the latter being two small bodies lying on the anterolateral surface of the aorta just below the point of origin of the inferior mesenteric artery. Tumors arising from the organs of Zuckerkandl are rare, as is stressed in a recent review of the literature by Ortega.[1] He found 15 cases reported to date, and in only eight of these was there a clinical picture of an actively secreting tumor present. In only one case, reported by Bauer and Leriche,[2] was the tumor successfully resected, but in this case, a 40 year old male, the blood pressure remained constantly elevated following resection.

The following case is reported as one of a secreting paraganglioma of the organ of Zuckerkandl which was successfully resected, with a subsequent return of the blood pressure to normal levels.

Case Report

A 27 year old female was admitted to The Montreal General Hospital on April 3, 1951. Her complaints on admission were palpitations, loss of strength and shortness of breath on exertion for six months. Inquiry revealed, however, that even as a child she had been unable to participate in sports because of attacks of palpitations and shortness of breath. At the age of 19 she consulted a physician because of frequent crying spells and nervousness. She was told at that time that she had a goiter, although she had noted no neck enlargement. Iodine in the form of Lugol's solution was given for a period of six months, without noted relief. The patient consulted another physician in March, 1951, and a basal metabolic rate determination which was made was reported as plus 26. She was again placed on iodine medication, and thiouracil therapy was being contemplated when she was seen in consultation by one of us and hospital admission was advised for further investigation. There had been a progressive weight loss of six pounds during the six months prior to admission.

Physical examination on admission revealed a thin, pale young girl who appeared very tense. There were no eye signs of thyrotoxicosis and no unusual tremors of the extended hands. The thyroid was not palpably enlarged, nor was there a bruit over the gland. There was a marked tachycardia, with a pulse rate of 125 per minute. A Grade II systolic murmur was heard over the pulmonic area. The heart was not clinically enlarged. Blood pressure was 150/104 mm. of Hg in the lying position. Examination of the abdomen revealed a firm, egg-sized mass lying to the right of the umbilicus which was freely movable toward the midline. It was nontender and did not appear to be related to the right kidney. Squeezing manipulation of this tumor on two occasions produced the following changes in blood pressure:

	First attempt	Second attempt
Resting	188/118	180/110
Start of massage	158/110	140/110
After 1 min. of massage	250/132	280/140

The second attempt at manipulation of the tumor (figure 1) produced a sudden onset of a severe pounding headache over the sinciput and an extreme sense of anxiety. The danger of this manipulation has been stressed by others.

Laboratory data: A basal metabolic rate determination was plus 33. Plasma cholesterol was 151 mg. per 100 c.c. The patient was given a tracer dose of 500 microcuries of I^{131}. Total urinary excretion of I^{131} at the end of 48 hours was 83.4 per cent of the total dose. A direct counter reading over the abdominal tumor showed no uptake of the radioactive iodine. Benzodioxane, in the dosage of 0.25 mg. per kilogram of body weight injected intravenously, produced a fall in blood pressure from 212/135 to 160/90 mm. of Hg within 30 seconds of the injection. A

barium series revealed an extrinsic deformity of the duodenum at the level of L-4, L-5. An intravenous pyelogram was normal. During the preoperative course in hospital, daily blood pressure readings averaged 185/115 mm. of Hg.

Operative Data: On the tenth hospital day a laparotomy was carried out through a right rectus incision under intravenous Pentothal and nitrous oxide gas anesthesia. The tumor was found situated in the retroperitoneal space just to the right of the bifurcation of the aorta. It was attached by interstitial tissue along the aorta and right common iliac artery, drawing its blood supply from the right common iliac artery. During exposure of the tumor the blood pressure rose to 250/105 mm. of Hg. Immediately upon clamping the blood supply of the tumor, the blood pressure fell precipitously to 90/60 mm. of Hg. An intravenous epinephrine drip (containing 8 micrograms of epinephrine per milliliter) was started and the blood pressure was stabilized at 130/80 mm. of Hg, with the drip running at 2 to 3 c.c. per minute (figure 1). The tumor was successfully resected.

Postoperative Course: Postoperatively the epinephrine drip was continued for 32 hours, and when it was discontinued the blood pressure stabilized at 115/75 mm. of Hg. The patient was out of bed on the fifth postoperative day without hypotensive complications. A basal metabolic rate done on the twelfth postoperative day was minus 2. An interesting series of electrocardiograms was taken preoperatively, and

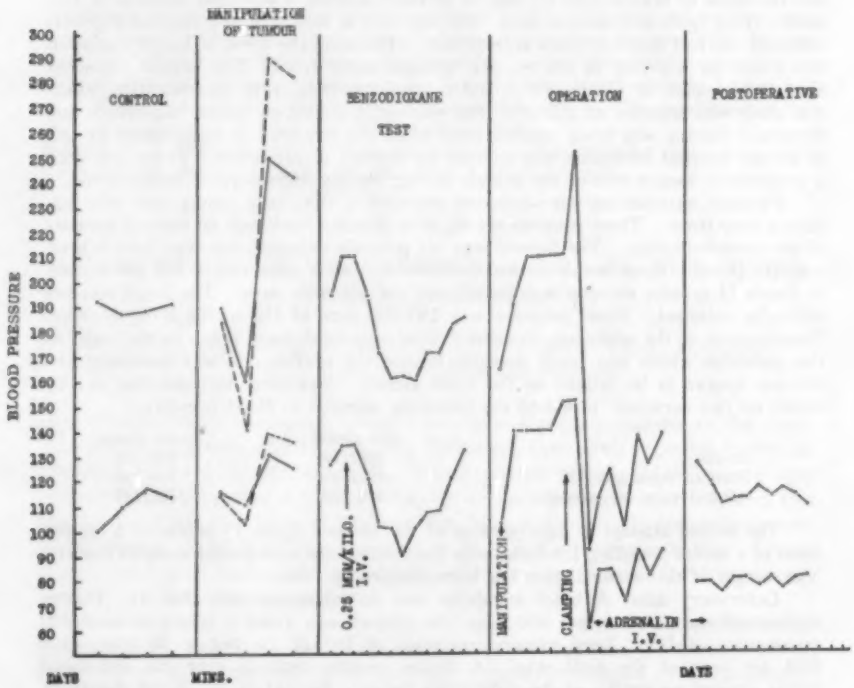


FIG. 1. The blood pressure record of a case of a functional paraganglioma, showing the changes induced by squeezing of the tumor, a benzodioxane response, and, finally, removal of the tumor.

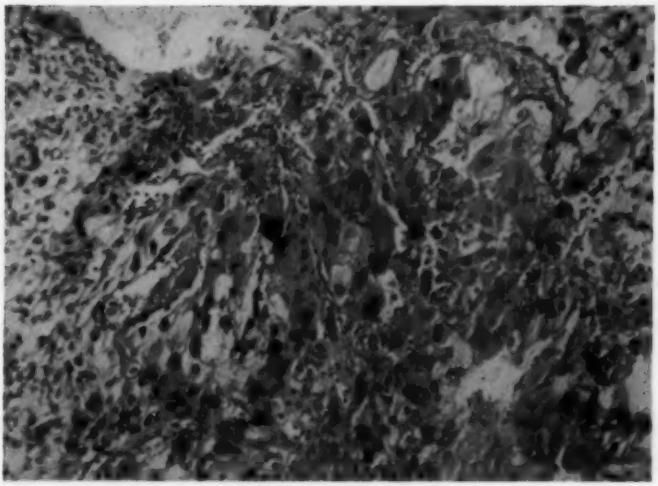


FIG. 2. A photomicrograph of the resected paraganglioma (× 112). Note the extreme pleomorphism of the nuclei and cellular outlines.

one and a half hours, 36 hours and three days postoperatively. The preoperative tracing revealed a left axis deviation. One and a half hours postoperatively a negative T wave in Lead I, with flattening of the T waves in the precordial leads, indicated a degree of left ventricular strain. These changes were accentuated in the record taken 36 hours postoperatively. Three days postoperatively the records showed a return toward a normal tracing.

Preoperatively the patient was found to have a considerable degree of hypochromic normocytic anemia, but we did not feel preoperative blood transfusions were indicated because of possible deleterious circulatory effects. Postoperatively, iron medication by mouth was instituted but had to be discontinued because of gastrointestinal upset. The serum iron was determined at 1 gamma per 100 c.c., and the unsaturated iron binding capacity of the serum was found to be 250 gamma per 100 c.c. With the combination of a low serum iron and a high normal unsaturated iron binding capacity, the anemia was felt to be of the true iron deficiency type. Consequently the patient was started on intravenous iron therapy, using a disaccharated oxide of iron preparation. In all, the patient received 1,500 mg. of elemental iron by this route over a period of eight days. At the end of this period the hemoglobin values had risen from 9.3 to 12.1 gm. per cent, with a reticulocytosis of 4 per cent persisting at the termination of therapy.

Pathologic Findings: Microscopic examination showed the tumor to consist of pleomorphic cells which in general were large and irregularly polyhedral in shape, with cytoplasm ranging from eosinophilic ground-glass to reticulate, multivacuolate and foamy. Nuclei in general tended to be vesicular, with the chromatin finely dispersed. A single nucleolus was generally present (figure 2). A noted feature of the microscopic examination was the arrangement of the tumor cells around thin-walled blood vessels of the tumor. About these vessels the cells tended to be columnar and arranged in a radial pallisading manner (figure 3). The brownish pigmentation of the cells, seen when chromate fixatives were used, was most heavily concentrated around these blood vessels.

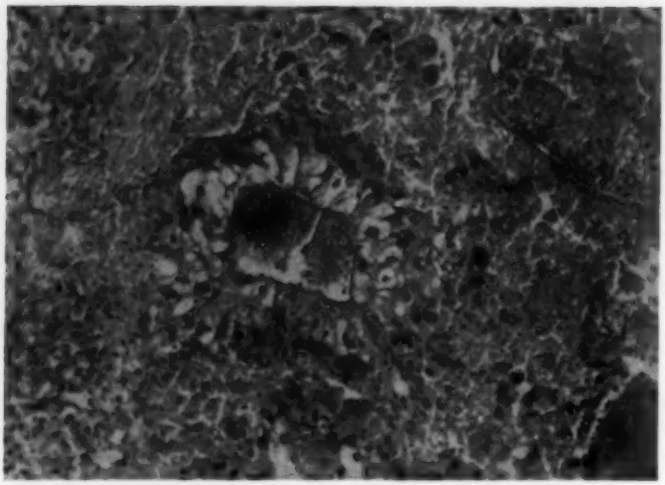


FIG. 3. A photomicrograph of the resected paraganglioma (× 112). Note the columnar cells arranged in a pallisading manner around the thin-walled vascular space.

Follow-up Course: The patient has been followed at regular intervals during a two-year period since operation. She continues asymptomatic and normotensive.

COMMENT

A case of a functional paraganglioma has been presented with successful resection, the patient becoming normotensive following operation and remaining so during a two-year follow-up. A review of the literature would suggest that this may be the first such case to be reported.

The similarity of the clinical picture of adrenal medullary hyperfunction (as this case exhibits) and thyrotoxicosis should be stressed. Williams [3] has stated that suspicion of the presence of a pheochromocytoma should be aroused if a patient has chronic hypertension and an elevation of the basal metabolic rate which regularly exceeds plus 30 per cent, without persistent enlargement of the thyroid gland. The above case demonstrates all these features. However, in recent years further adjuvants in the differential diagnosis of these two conditions have come into general use, namely, the determination of rates of uptake or excretion of radioactive iodine. In the above case we were able to demonstrate that the total excretion of I^{131} was not depressed; nor was there any uptake of the radioactive iodine by the palpable abdominal tumor. Thus we were able to exclude the thyroid as the source of the hypermetabolism manifested by the elevated basal metabolic rate, the low serum cholesterol value and the history of weight loss.

Finally, it should be noted in this case that squeezing manipulation of the paraganglioma on two occasions produced an initial and definite fall in blood pressure, to be closely followed by the rapid rise characteristic of these tumors.

This initial fall in blood pressure has not been previously commented upon and is as yet unexplainable.

ACKNOWLEDGMENT

The authors are indebted to Dr. Howard Root, of the Department of Pathology of The Montreal General Hospital, for his assistance in preparing the pathologic report and the photomicrographs used in this presentation.

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THE DEVELOPMENT OF ACUTE MYELOGENOUS LEUKEMIA IN A PATIENT WITH RETICULUM CELL LYMPHOMA *

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SINCE Sadler's [1] original description of leukemia in a patient with a "round cell sarcoma" there have been many reports of cases of malignant lymphoma terminating in leukemia. The dominant cell type of these leukemias has been a variety of mononuclears such as large lymphocytes or stem cells,[2–7] small lymphocytes,[5, 6, 8–12] "lymphosarcoma cells" or "leukosarcoma cells," [2, 13–18] unspecified types of mononuclears [19–23] and monocytes.[9] To our knowledge, however, no case of myelogenous leukemia has ever been reported in any patient with a malignant lymphoma.

CASE REPORT

A 19 year old male college student was admitted to The University of Chicago Clinics in June, 1949. In August, 1948, he had first noticed a lump in the left groin. The following month a lymph node biopsy at another hospital was reported to show marked hyperplasia and an area of suppuration. In May, 1949, the mass was noted to recur and to grow rapidly in size, and the patient was admitted to the Surgical Service of the late Dr. Dallas B. Phemister at The University of Chicago Clinics.

Physical examination on admission was normal except for the presence of a hard, irregular, firmly fixed left inguinal mass. There was no other lymphadenopathy. The liver and spleen were not palpable. There were 16.5 gm. of hemoglobin, 5.43 million red blood cells and 5,900 white blood cells, with 62 per cent polys, 33 per cent small lymphocytes, 1 per cent monocytes and 4 per cent eosinophils. At surgery a matted mass of lymph nodes was found to involve the femoral vein, which had to be sacrificed. Considerable hemorrhage resulted, and 2,500 c.c. of blood were transfused at operation.

Microscopic examination of the pathologic specimen showed transitions between marked hyperplasia and reticulum cell sarcoma (figure 1). There was some fibrosis

* Received for publication September 14, 1953.
From the Argonne Cancer Research Hospital and Department of Medicine, University of Chicago.

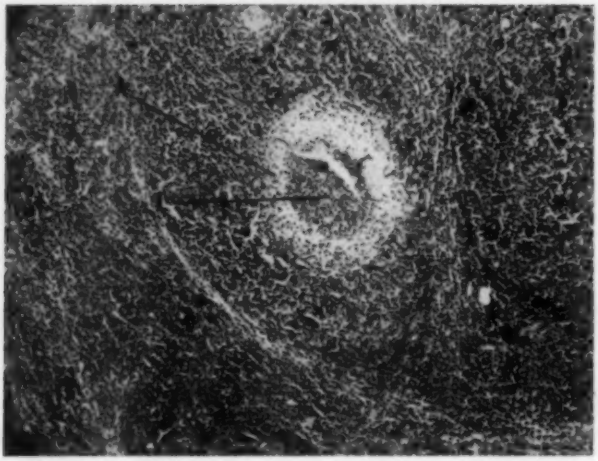


FIG. 1. Reticulum cell lymphoma removed from the left groin in June, 1949, showing infiltration of an arteriole (A) by lymphoma (L). Hematoxylin and eosin (× 70).

and eosinophilia, but no giant cells were present. The wall of the femoral vein was largely replaced by tumor cells (figures 2 and 3).

Postoperatively, gangrene of the left foot developed and in August, 1949, a disarticulation of the metatarsal bones was performed. Fatty marrow was present in the surgical specimen. In October, 1949, the patient became jaundiced and a diagnosis of homologous serum hepatitis was made. Two needle biopsies of the liver carried out during October, 1949, and a follow-up biopsy in July, 1950, showed no evidence of lymphomatous or leukemic infiltration.

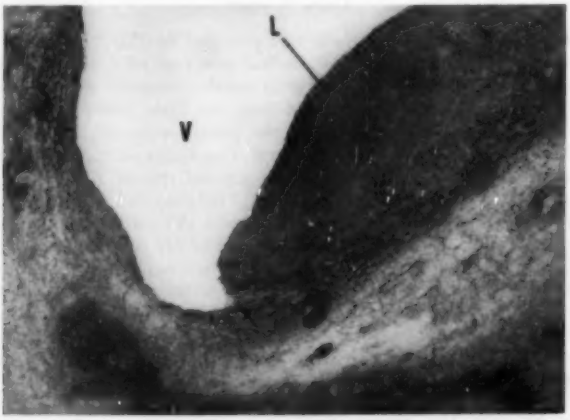


FIG. 2. Tumor tissue (L) encroaching on the lumen (V) of the femoral vein removed in June, 1949. Hematoxylin and eosin (× 7).

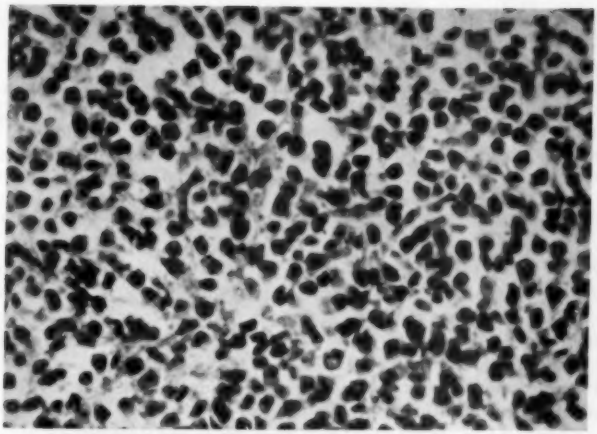


FIG. 3. A higher power view of tumor tissue shown in figure 2, showing it to consist of small reticulum cells. Hematoxylin and eosin (× 500).

The patient recovered rapidly and did very well for over a year. Some nodular induration was felt in the left groin. The peripheral blood picture remained normal. In February, 1951, although the patient felt quite well, the presence of a hard, irregular mass was noted in the abdomen, just above the region of the left inguinal ligament. In February, 1951, 2,100 r of x-ray therapy was given to this area, with considerable decrease in the size of the mass. In March, however, painful swelling of the left testis developed, and in May, 1951, an additional 600 r of x-ray was given to the left upper quadrant and a left orchiectomy was performed. Microscopic

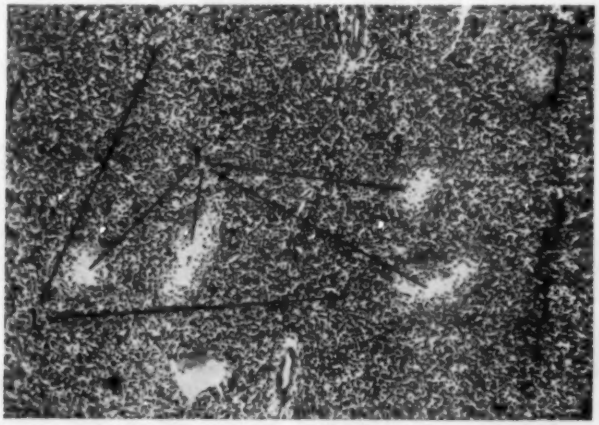


FIG. 4. A small portion of the left testis removed in May, 1951, showing only a few remaining testicular tubules (T), the remaining tissue all consisting of reticulum cell lymphoma (L). Hematoxylin and eosin (× 70).

examination revealed almost complete replacement of the testis by reticulum cell sarcoma (figure 4).

The patient again did very well until September, 1951, at which time he began to complain of left flank pain. On September 21, 1951, physical examination still revealed no lymphadenopathy. The liver and spleen were not palpable. There were 13.2 gm. hemoglobin, 4.42 million red blood cells, 0.4 per cent reticulocytes, and 5,000 white blood cells, with 85 per cent polys, 1 per cent eosinophils, 8 per cent small lymphocytes and 4 per cent monocytes. No abnormal cells were found in the peripheral blood. The platelet count was 200,000 (normal in this laboratory). Urinalysis was normal. Intravenous pyelogram showed no excretion of dye by the left kidney.

Between September 17 and October 13, 1951, 1850 r of x-ray therapy was given to the abdomen. Four white blood counts during October, 1951, all ranged between 1,400 and 2,500. Unfortunately, no differential counts were done. The hemoglobin remained unchanged. At this time the patient developed a mass in the right cheek, which was treated with 2,000 r from October 22 to November 3.

Within the next three weeks his amputation stump became ulcerated, generalized lymphadenopathy developed for the first time, the gums became swollen and ulcerated, and dyspnea occurred on exertion. On admission to the hospital on November 29, 1951, physical examination revealed marked lymphadenopathy involving all major groups of nodes. The skin contained numerous petechiae and ecchymoses. Retinal hemorrhages were present. The gingivae were swollen, dark and ulcerated. The right tonsil was covered with necrotic ulcerations. The liver and spleen were not palpable. The hemoglobin was now only 8.8 gm., with 2.97 million red blood cells and 0.6 per cent reticulocytes. The white blood count had risen to 42,000, with 3

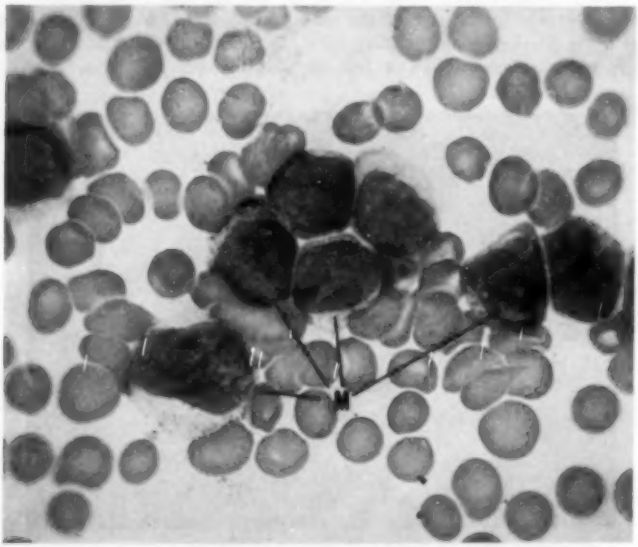


FIG. 5. A clump of myelocytes (M) in the peripheral blood, November 29, 1951. Wright's stain (× 1,060).

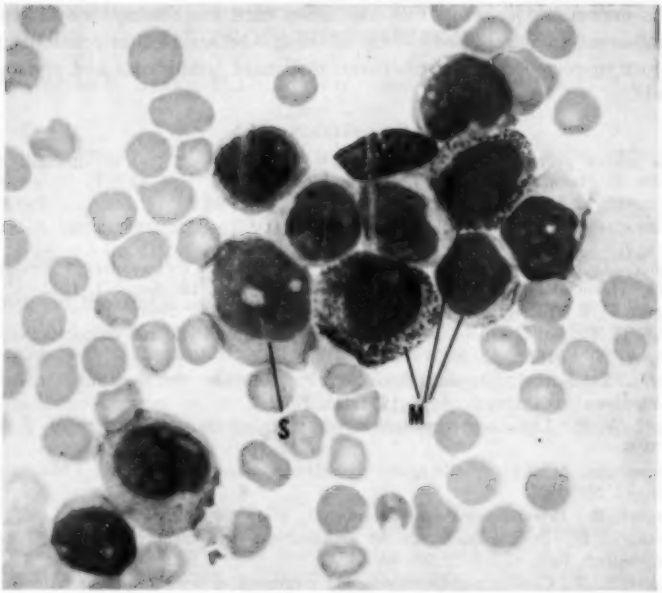


FIG. 6. A clump of myelocytes (M) and a stem cell (myeloblast) (S) in a smear of the sternal marrow, December 1, 1951. Wright's stain (× 1,060).

per cent neutrophils, 1 per cent eosinophils, 5 per cent small lymphocytes, 61 per cent stem cells, 19 per cent promyelocytes, and 11 per cent neutrophilic myelocytes (figure 5). The platelet count had fallen to 8,800. A sternal bone marrow smear was typical of acute myelogenous leukemia (figure 6). In spite of treatment with 200 mg. ACTH daily and the transfusion of 2,000 c.c. whole blood, the patient's course was rapidly downward. On December 12, 1951, the steadily rising white count had reached 190,000, with 2 per cent neutrophils, 67 per cent stem cells, 21 per cent promyelocytes, and 10 per cent neutrophilic myelocytes. The hemoglobin was 4.4 gm. On December 13, 1951, the patient became comatose and died. Permission for autopsy was refused.

DISCUSSION

Although permission for autopsy could not be obtained, there appears to be no reasonable doubt that acute myelogenous leukemia developed in this patient with a malignant lymphoma.

Such an occurrence might be explained by postulating that a multipotential stem cell had changed its direction of differentiation from the lymphatic to the granulocytic series. A chance association of these two diseases does not appear too improbable, however, since it has been demonstrated that exposure to ionizing radiations increases the incidence of leukemia in man.[24] Indeed, because their coexistence has not been reported before, this alternative seems the more likely one.

It is important, however, that any other such cases which may have come under observation be reported to help establish whether a closer relationship than heretofore suspected does exist between malignant lymphomas and myelogenous leukemia.

ACKNOWLEDGMENTS

The author gratefully acknowledges the helpful advice of Dr. W. Bethard, Dr. M. Block, Dr. E. Humphreys and Dr. L. O. Jacobson.

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THYROID CRISIS SUBSEQUENT TO WITHDRAWAL OF PROPYLTHIOURACIL *

By THOMAS R. KELLY, M.D., and THEODORE L. BLISS, M.D., F.A.C.P.,
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THE occurrence of a fulminating and fatal thyroid crisis subsequent to the withdrawal of propylthiouracil used to control hyperthyroidism is the basis of this report. The thyroid-blocking drugs have gained wide acceptance as a preparation for surgery and as a definitive method of treating hyperthyroidism. In the latter use its withdrawal may be followed by relapse after variable intervals. We were unable to find a report of thyroid crisis occurring at an interval subsequent to the withdrawal of a thyroid-blocking drug. Nelson et al.[1] have reported death due to thyroid crisis a few days after the administration of radioactive iodine for the treatment of hyperthyroidism. Pollard [2] reported a death in thyroid crisis in a patient who developed granulopenia and agranulocytosis during a second course of propylthiouracil given to control hyperthyroidism. The drug was withdrawn 36 hours before death, which was attributed to the toxic effects of the drug and thyroid crisis.

CASE REPORT

In 1946 the patient, a 24 year old white female, noticed protrusion of the left eye during the second trimester of her second pregnancy. Within a few months after this pregnancy, the right eye protruded. One year later (1947), during her third pregnancy, she became very nervous and developed a ravenous appetite, a tremor and heat intolerance. A basal metabolic rate was plus 75 per cent. Iodine was prescribed in preparation for surgery, which the patient refused.

In 1948 she was admitted to the Johns Hopkins Hospital.† At that time she had a ravenous appetite, a marked tremor, was unable to sit or to remain still, and had generalized muscular weakness. She had noted enlargement of her neck and had palpitation of the heart. There had been no history of dyspnea or ankle edema.

On physical examination the temperature was 98.6° F., the pulse 130, respirations 22, and the blood pressure 132/50 mm. of Hg. She was thin and markedly hyperactive; the skin was moist, and the hair was of fine texture. The palpebral fissures were widened, and she had a glassy stare and infrequent blinking. There was a lid lag, the forehead did not wrinkle on upward gaze, and convergence was poor. Her teeth were carious and the gums were inflamed. There was a gross and a fine tremor of the tongue. The thyroid gland was diffusely enlarged and firm, with no discrete nodules, and the right lobe was larger than the left. There was a loud systolic bruit over the entire gland. The chest was normal on physical examination. The heart was not enlarged on percussion, and there was a grade II systolic murmur in the aortic and pulmonary area. The remainder of the examination was negative.

Laboratory data showed the blood count, urinalysis and the blood nonprotein nitrogen, sugar, proteins and calcium to be within normal limits. The sedimentation rate was 38 mm. in one hour. The blood phosphorus was 5.5 mg. per cent; cholesterol, 223 mg. per cent; basal metabolic rate, plus 76 per cent. The electrocardiogram was normal. Exophthalmometer readings were 18 mm. in both eyes. A diagnosis of diffuse toxic goiter was made. Thyroidectomy was again advised but the patient refused surgery.

* Received for publication October 9, 1953.
† We are indebted to Dr. John E. Howard for a transcript of that record.

The patient was placed on a 3,000 calorie diet, bed-rest and phenobarbital, 32 mg. three times a day. On the third hospital day propylthiouracil, 300 mg. divided into four doses, was started. On the ninth day of treatment the basal metabolic rate was plus 45 per cent and the pulse rate was 88. During 11 hospital days the patient was afebrile and her weight remained unchanged. She had considerable subjective improvement on this régime.

In December, 1948, four months later, she returned to the Johns Hopkins Hospital. There had been further weight loss and only minimal symptomatic improvement. The proptosis and tremor of the fingers were more marked, and she was unable to sit still for a moment. The pulse was 140 and regular and the blood pressure was 140/60 mm. of Hg. A large soft nodular thyroid with palpable thrill over both upper poles was present. There was no edema. The basal metabolic rate was plus 54 per cent and the serum cholesterol was 148 mg. per cent. The impression at that time was severe thyrotoxicosis, unrestrained by 300 mg. of propylthiouracil daily, and the dose was increased to 500 mg. daily. She was told to return in three months.

In February, 1949, the blood pressure was 120/70 mm. of Hg and the pulse rate was 112. The basal metabolic rate was plus 30 per cent and the serum cholesterol was 220 mg. per cent. The patient appeared to be considerably improved and was told to continue propylthiouracil, 500 mg. daily, and to return in three months.

From February, 1949, to September, 1951, when she entered the City Hospital of Akron, the patient had no medical attention. Her condition had so improved on 500 mg. of propylthiouracil daily that she had stopped her medication voluntarily in March, 1951, and by history was euthyroid.

At the time of her admission to the City Hospital of Akron her husband stated that she had remained well until 10 days before, when she became nervous and progressively short of breath. Three days before admission her symptoms became worse and she developed diarrhea and soreness of her arms and legs. On examination the blood pressure was 142/60 mm. of Hg, the temperature 101° F., and the pulse was irregular and too rapid to count accurately. She was thin, apprehensive and exceedingly restless, and exhibited muscular weakness of all extremities. Her eyes showed a marked exophthalmos. Her skin was hot, flushed and moist. Her tongue was dry and coated and there was moderate inflammation of the gums but no evidence of tonsillitis. The thyroid was diffusely enlarged, the right lobe more so than the left, and was firm and contained no nodules. There was a loud systolic bruit over the thyroid. Her chest was clear to percussion and auscultation. Her heart was enlarged slightly to the left on percussion and was in auricular fibrillation. There was a grade II systolic murmur, heard best at the apex. There was some swelling in the calves, but no pedal edema. A diagnosis of thyroid crisis was made.

Laboratory examination revealed a protein-bound iodine of 12 micrograms, a blood sugar of 20 mg. per cent, and a serum cholestrol of 120 mg. per cent. The blood calcium, potassium and phosphorus were all within normal limits. The basal metabolic rate was plus 95 per cent. Before any treatment could be instituted she became markedly dyspneic and died suddenly, one hour after admission. Permission for an autopsy was refused.

Discussion

McArthur, Means, Rawson and Cope [3] have reported the occurrence of 36 cases of thyroid crisis in 2,033 cases of hyperthyroidism admitted to the Massachusetts General Hospital between 1921 and 1946. Twenty-four of the 36 patients having crisis died. Among the patients who developed thyroid crisis following surgery the most frequent precipitating factors were the operation and bronchopneumonia. Among nonsurgical patients developing thyroid

crisis the most frequent precipitating factors were iodine withdrawal and digitalis intoxication. Their report was made prior to the widespread use of thyroid-blocking drugs.

Several theories explaining the development of thyroid crisis have been presented. Levy [4] showed that the excessive production of thyroxin increased the sensitivity of the sympathetic nerve endings to the action of adrenalin. Thus, should a patient with hyperthyroidism be subjected to an additional stress such as trauma, infection or emotional strain which increased his adrenalin secretion, there might be overstimulation of the sympathetic nerve endings and crisis could ensue.

Since 1905 many investigators have called attention to the pathologic changes in the liver associated with hyperthyroidism. Kuriyama [5] showed that feeding desiccated thyroid to rats caused a depletion of the glycogen content of the liver within three to five days. Haban [6] made similar observations in cats and noted necrotic changes in the liver. Lahey [7] believes deaths due to hyperthyroidism are chiefly liver deaths, and effectively uses glucose intravenously in combating the excessive combustion of glucose that results from hyperthyroidism. It is also known that the patient with hyperthyroidism has an oxygen demand increased two- to threefold which predisposes to anoxic anoxia. The liver especially is vulnerable to anoxia, since only 25 per cent of its blood supply is arterial. Under such conditions of hepatic anoxia the damaged liver appears to accelerate the thyroid gland to hyperactivity. Ficarra et al.[8] postulated that hyperadrenalism in the hyperthyroid patient caused liver glycogen depletion, and that in this state of insufficiency the hepatic anoxia caused by hypermetabolism may precipitate the thyroid crisis.

Lahey [9] explains that the state of excessive combustion in hyperthyroidism is offset by an increased intake of fuel. As long as there is a balance between food and fluid intake and the increased combustion, the hyperthyroid patient is able to survive. If the food and fluid intake fails due to vomiting and diarrhea, there is progressive autocombustion of the available glycogen and depletion of the glycogen reserve in the liver, and thyroid crisis may ensue.

The danger signal of impending crisis is an increase in the clinical symptoms of thyrotoxicosis. The patient may complain of increased irritability and restlessness. Sweating may be more pronounced and respiration irregular. The pulse rate will increase, and with the onset of vomiting or diarrhea thyroid crisis is imminent. The temperature will rise as glycogen reserve is depleted. If a fever is present from the start, one should search for a coexisting infection which, in Lahey's [9] experience, is most often tonsillitis. If the cycle progresses, there will be confusion, delirium and coma. The heart rate continues to increase, and auricular fibrillation is not infrequent.

The basal metabolic rate and protein-bound blood iodine are increased in direct proportion to the toxicity of the patient, although exceptions to the rule are found. The serum cholesterol as a rule is inversely proportional to the toxicity. Maddock [10] and his co-workers found essentially normal values for the inorganic ions of the blood such as phosphorus, potassium, sodium and calcium. Patients with hyperthyroidism have a tendency to hyperglycemia, due to the mobilization of the available carbohydrate. If thyroid crisis develops, the mobilized carbohydrate will be exhausted and hypoglycemia results. Holman [11]

reported that one to two hours after thyroidectomy there is hyperglycemia, since this is the period when the greatest mobilization of carbohydrate takes place. This is followed by an abrupt fall in the blood sugar during the next 24 to 36 hours.

The patient whose case is reported here had had a severe hyperthyroidism for which she refused surgery. Relatively large doses of propylthiouracil had controlled her disease so effectively that she discontinued the drug voluntarily. Apparently she remained well until 10 days before her death. The relapse, which culminated in crisis and death, occurred without demonstrable trauma, infection or emotional strain. The laboratory findings on admission were typical of those found in crisis, including an extremely low blood sugar (20 mg. per cent). Most of the reports were returned after the patient had died. The fulminating and explosive character of her fatal illness gave us the impression that there had been a sudden release from control of her hyperthyroidism. This, of course, is purely speculative, but it may represent a danger inherent in the withdrawal of thyroid-blocking drugs. One could speculate further as to whether repeated clinical and laboratory observations during the six-month interval between the withdrawal of the drug and death would have revealed a beginning relapse. The history, however, did not so indicate. At any rate, it might be advisable to observe patients closely and for a long period after the withdrawal of a thyroid-blocking drug when it has been used to control hyperthyroidism.

Conclusions

A fulminating and fatal case of thyroid crisis that occurred subsequent to the withdrawal of propylthiouracil used to control hyperthyroidism has been presented.

The factors leading up to thyroid crisis have been discussed.

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FATALITY FOLLOWING PENICILLIN INJECTION*

By SEYMOUR FISHER, M.D., *Phoenix, Arizona*

THE use of penicillin is so common, and fatal reaction to the drug so rare, that such an end result is of interest to the profession. The following case is interesting in that death occurred almost instantaneously in a seemingly healthy individual with no apparent allergic background.

CASE REPORT

History: This 28 year old white male was admitted to the Veterans Administration Hospital, Phoenix, Arizona, on July 21, 1953, for correction of a right fifth hammer toe, present since birth. A complete history and physical examination showed no significant abnormalities other than the hammer toe.

Laboratory: Routine blood, urinalysis and chest x-ray were all within normal limits.

Course in Hospital: On July 23 the patient was scheduled for surgery, and at 8:30 a.m. was given Demerol, 100 mg., and atropine sulfate, gr. 1/150. At 9:15 a.m. he received a low spinal anesthetic consisting of 150 mg. of procaine. The operation was started at 9:23, and consisted of a disarticulation of the right fifth toe at the metatarsal phalangeal joint. Blood pressure and pulse were normal throughout. The patient was returned to the ward at 9:55 a.m., at which time he was talking with the anesthetist and his mother. A few minutes after returning to the room he was given a drink of water which was at room temperature. The anesthetist at this time checked the level of anesthesia and found that it had receded. A few minutes later (at 10:05 a.m.) the patient was given a prophylactic injection of 300,000 units aqueous penicillin intramuscularly in the arm. In less than five minutes the mother reported to the nurse that the patient complained of chest pain. The nurse immediately went to the patient, who then complained of shortness of breath, stating that the pain had subsided. Within seconds he became cyanotic and pulseless. At 10:10 a.m. a second nurse administered 1 c.c. of adrenalin intramuscularly, and artificial respiration was started. This was followed by Coramine, oxygen under positive pressure, adrenalin into the heart and, finally, a mechanical respirator. At 11:00 a.m. all efforts were discontinued and patient was pronounced dead.

Following this incident, additional history was obtained from the family to the effect that several years ago, on two different occasions, the patient had had two severe local reactions to Novocain, necessitating discontinuance of operative procedures. Penicillin (type unknown) had been given on several occasions for minor illnesses, without reactions.

Autopsy Findings: Autopsy was performed five hours after death. The embalmed body was that of a young, well developed, well nourished white male measuring 165 cm. in length and weighing approximately 165 pounds. The findings in the main were negative. The subcutaneous fat was generally increased, measuring up to 2.0 cm. over the thorax and 4.0 cm. over the abdomen. The intra-abdominal lymph nodes were not enlarged. The mesenteric lymph nodes were moderately enlarged, yellowish gray in color and rubbery in consistency, but on section showed no gross alterations.

The right lung weighed 325 gm.; the left, 350 gm. They appeared slightly collapsed and were moderately doughy in consistency. The blood content of all lobes

* Received for publication December 22, 1953.
From Veterans Administration Hospital, Phoenix, Arizona.

of the lungs was generally increased. There was no evidence of edema fluid or areas of increased density. The blood generally was a dark red color and was fluid, with no evidence of clotting. The tracheobronchial tree had a moderately thickened wall and somewhat edematous, thickened and reddened mucosa. The mucosa was covered by a thin layer of mucus. There was no evidence of obstruction of the respiratory tract. The intrapulmonic branches of the bronchi had moderately thickened walls and some narrowing of their lumens. The tracheobronchial and hilar pulmonary lymph nodes were irregularly and slightly enlarged and grayish black in color, and on section the deposits of black pigment obscured the architecture.

The lumens of the coronary arteries appeared moderately smaller than expected for a heart of this size. In the interventricular septum and in some areas of the left ventricle there were tiny grayish areas of focal fibrosis associated with the vessels of the heart. The aorta generally showed a normal elasticity and no remarkable change of the components of the wall; however, the cross sectional area was approximately one third of the normal for a patient of this size. Measurements averaged 1.3 cm. in diameter. The peripheral arteries generally showed a smaller cross sectional area than normal.

The spleen was somewhat enlarged, weighing 225 gm. The capsule was gray and the splenic parenchyma soft in consistency. On section the red pulp was dark and moist, with an accentuation of the splenic follicles against the dark red background. The liver weighed 1500 gm. and was normal in size and shape. The capsule was smooth, shiny and transparent. On section the parenchyma had an increased blood content and was a reddish brown color. The architecture was moderately obscured. The right adrenal was made up of two parts: the upper pole measured 3.5 by 2.5 by 2.5 cm. and presented a multicolored cystic appearance, and was irregularly covered by thin, somewhat filmy, yellowish adrenal cortex; the remainder measured 4 by 3.5 by 0.7 cm., and on section showed essentially normal structure. The left adrenal measured 5.5 by 4.5 by 0.5 cm. and had a normal cortical and medullary area. The esophagus was not remarkable. The stomach was moderately dilated, the serosal surface smooth but slightly opaque, and on section the mucosa was thickened, reddened and edematous, with an accentuation of the rugae. The duodenum, jejunum, ileum, cecum and colon showed similar congestive changes. The mesenteries showed no remarkable changes except for a slight increase in fatty tissue.

The dura was adherent to the pia in a small area on the convexity of both cerebral hemispheres. The brain weighed 1,300 gm., and the vessels of the pia arachnoid regions were prominent and filled with dark fluid blood. The gyri showed slight flattening, the sulci some narrowing and deepening. On section the cerebral hemispheres appeared moderately congested and slightly swollen. The ventricular system showed no remarkable changes. The basal ganglia, pons, medulla and cerebellum appeared congested and, with the medulla, there was a rather indistinct area of softening which may have been associated with incomplete embalming. The hypophysis appeared congested.

Microscopic Findings: A section through a bronchus showed a moderately thickened respiratory mucosa, with active mucus production and a moderately thickened, partially hyalinized basement membrane. The submucosa showed a considerable edema, with a dilatation of the capillaries and lymphatic channels and a slight, lymphocytic infiltration and an occasional eosinophilic leukocyte. Sections of the lungs showed a generalized congestion of the parenchyma. Many of the alveolar sacs contained pink-staining, albuminoid material. The bronchioles showed a generalized mucosal hypertrophy with considerable mucus production and accentuated, thickened, hyalinized basement membranes similar to the bronchus. The alveolar pattern was variable in some areas, with thickened, alveolar walls, ruptured septal walls with club-shaped ends, and intercommunication of the alveoli in the area.

A section through the interventricular septum of the heart showed a moderate intimal thickening of the coronary artery in the section with a narrowing of the lumen. This area of intimal thickening showed some lymphocytic infiltration and an occasional eosinophil. There appeared to be no duplication of the internal, elastic membrane in this section. The myocardial fibers showed superficial fatty infiltration and separation.

A section of the spleen showed a generalized congestion of the parenchyma with an accentuation of the splenic follicles. Within the sinusoids there were moderate numbers of eosinophils. The liver showed moderate congestive changes, with a dilatation of the central veins and sinusoids and some deposits of bile pigment within the neighboring hepatic cells. Within these areas also were varying sized, clear vacuoles representing fatty infiltration. The portal spaces were not remarkably altered. In one area there was a cross section of the pancreatic duct which showed a moderate periductal lymphocytic infiltration. A section of the left adrenal showed no remarkable changes. A section through the right adrenal showed an alteration of the structure by the production of multilocular, thick-walled cysts. The cyst walls were composed principally of proliferated, hyalinized, fibrous connective tissue which, in one area, showed focal calcification. The remnants and islands of the adrenal cells showed no remarkable changes other than foci of lymphocytic infiltration. Sections of the kidneys showed generalized congestion of the parenchyma, with larger and smaller cortical areas with an obliteration and hyalinization of the glomerular structures, atrophy of the tubules, fibrosis and lymphocytic infiltration. An occasional tubule contained a pink-staining, hyaline cast. In some areas along the collecting tubules there were foci of lime salt deposits. Some of the glomeruli were in the process of hyalinization and presented a wire-loop type of picture. These glomeruli showed a loss of the nuclear structure. Many of the proximal and distal convoluted tubules were lined by cells with swollen, granular cytoplasm, others by clear cells.

Sections of the brain showed considerable congestion and edema. These changes were present in the cerebral cortex, basal ganglia, medulla, pons and cerebellum. No other remarkable changes were observed. A section through a small lymph node showed no remarkable changes other than a slight reticular hyperplasia.

Comment

It is quite well known that penicillin produces reactions in approximately 5 to 10 per cent of individuals. These reactions may be divided into types as follows: (1) urticarial or serum sickness, (2) erythematous, or (3) anaphylactic. They may further be divided into cause such as (1) Jarisch-Herxheimer, (2) severe allergic delayed, and (3) anaphylactic-shock.[1]

The number of deaths reported in the literature directly attributable to anaphylactic shock due to penicillin varies from two in October, 1952, to 17 in October, 1953. The differences appear to be a result of interpretation of the cause.

In view of the excellent discussions of the subject during the past year, especially by Higgins and Rothchild,[2] Feinberg et al.[4] and Kern and Wimberley,[3] none will be made in this paper.

The autopsy findings, as in other reported cases, were of little significance. There was an increased amount of subcutaneous fat. This was also noted in the case reported by Christenson et al.[5] The relationship of this to the reaction reported is as yet unknown; however, it may have significance, since it has been noted during the past two years that there is a greater tendency for reactions of all types to occur postoperatively in those individuals with a fat diathesis.

I am in accord with those authors who state that antibiotics should be used only when indicated, and not as a prophylactic or "shotgun" medicament.

The treatment of the anaphylactic reaction is that of shock and is an emergency, testing the experience and ability of those in attendance.

Conclusion

A case is presented of an individual who was subjected to an apparently minor operation but who died within minutes after receiving an intramuscular injection of penicillin.

Acknowledgment

I wish to express my gratitude to Robert E. Campbell, M.D., Pathologist, Veterans Administration Hospital, Phoenix, Arizona, for the minute postmortem examination, and to Wallace A. Reed, M.D., Phoenix, Arizona, and to J. T. Boone (M.C.), Vice-Admiral U. S. N. (Ret.), Chief Medical Director, Veterans Administration, for comments on the clinical and pathologic aspects, together with concurrence in the conclusions as to cause of death.

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SPONTANEOUS REMISSION OF DIABETES MELLITUS: "THE HOUSSAY PHENOMENA IN MAN" *

By Marvin E. Levin, M.D., *St. Louis, Missouri*

The spontaneous remission of diabetes mellitus is an uncommon occurrence. Glassberg [1] has discussed the questionable "cures" of diabetes mellitus. He called particular attention to "cures" in obese diabetics following weight reduction, and noted remission of diabetes following treatment of thyrotoxicosis, development of cirrhosis of the liver, acromegaly following treatment, and of one case in which new islet cells were believed to have been formed.[2]

One other situation in which diabetes mellitus appears to be "cured" is following the development of hypopituitarism. Houssay [3] clearly showed this pancreatic-pituitary relationship when he was able to alleviate the diabetes in pancreatectomized dogs by hypophysectomy.

* Received for publication September 29, 1953.
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A case of diabetes mellitus is presented here, apparently cured by the onset of hypopituitarism. The spontaneous occurrence of this in man is extremely rare. Balfour and Sprague,[4] in consulting the files of the Mayo Clinic for 15 years up to 1949, could find no true case of naturally occurring diabetes relieved by hypopituitarism. They have reported two cases of diabetes secondary to acromegaly, in which the diabetes was relieved in one by radiation of the pituitary, and in the second by subsequent occurrence of meningitis.

In a review of the literature only eight well authenticated cases of spontaneously occurring Houssay phenomena in man have been reported.[5, 6, 7, 8, 9, 10, 11, 12] Of the six cases who died the immediate cause of death in three was hypoglycemia. The most frequent finding in the cases which came to autopsy was necrosis or infarction of the pituitary. Two of the cases[9, 10] occurred in women with a history compatible with Sheehan's syndrome[13] (pituitary insufficiency following childbirth in which there were associated shock and excessive blood loss). In one of these cases, reported by Poulsen,[12] there was remission of the diabetic retinopathy five years following the postpartum hemorrhage and onset of hypopituitarism.

Case Report

A 56 year old white male lawyer was admitted to Barnes Hospital on November 11, 1952, because of frequent insulin reactions. Polyuria, polydipsia and weight loss had led to a diagnosis of diabetes mellitus in 1937; treatment was instituted, and he had been well controlled on insulin and diet. For the past several years he had taken 50 units of protamine zinc insulin daily. Acidosis had not occurred, and insulin reactions had been infrequent. He had maintained his weight and had been active. In July, 1952, the patient had a cerebral vascular accident characterized by semiconsciousness for several days. Following this he had noted weakness in his right arm and inability to write; there was some regurgitation of liquids through his nose, and difficulty in articulation. Following this episode he has had gradual improvement of his neurologic signs and symptoms. However, he had noted a tendency to be cold, to use more blankets than before and to perspire less. Libido decreased and he had difficulty in obtaining an erection; however, pubic and axillary hair were retained. Repeated insulin reactions were experienced despite a reduction of his dose of insulin from 50 units of protamine zinc insulin to 20 units. Blood sugars at various times would be below 100 mg. per cent. None of these reactions was severe enough to cause syncope. The patient's family history revealed that his mother also had had diabetes. He had been taking large doses of methyltestosterone for several years for unknown reasons.

On physical examination, the blood pressure was 160/90 mm. of Hg lying and 115/80 mm. of Hg on standing. The patient was a well developed, well nourished man. The skin and the body and sexual hair were normal. The fundi showed moderately advanced arteriosclerotic changes and tortuosity of the arteries, and there was a moderate number of micro aneurysms and small exudates. The cardiorespiratory system was normal. There was slight atrophy of the testicles; the prostate was of normal size. Neurologic examination showed questionable weakness of the right seventh, ninth and twelfth cranial nerves. There was slight motor weakness of the right arm and grip and slightly decreased proprioception of the toes.

Laboratory data revealed no abnormality of the red and white blood counts, and the urinalysis was normal. The cardiolipin was negative. Radiogram films of the skull and chest were normal. An electrocardiogram was interpreted as an anteroseptal myocardial infarction, time uncertain (the patient had no history suggestive

TABLE I

Laboratory Findings

Glucose Tolerance Test		Water Excretion Test	
Fasting blood sugar	181 mg./100 ml.	Overnight specimen	360 ml. urine
1 hour blood sugar	332 mg./100 ml.	1 hour specimen	110 ml. urine
2 hour blood sugar	302 mg./100 ml.	2 hour specimen	85 ml. urine
3 hour blood sugar	258 mg./100 ml.	3 hour specimen	55 ml. urine
4 hour blood sugar	199 mg./100 ml.		
5 hour blood sugar	175 mg./100 ml.		

Eosinophil Test

	Control	4 hours
Epinephrine 0.3 ml. 1:1,000 s. c.	121 eos./cu. mm.	88 eos./cu. mm.
25 mg. ACTH intramuscularly	187 eos./cu. mm.	44 eos./cu. mm.

Plasma sodium	141 mEq./L.	BMR	−17%
Plasma potassium	5.1 mEq./L.	PBI	4.7 micro grams/100 ml. plasma
Plasma carbon dioxide combining power	30 mEq./L.		
Plasma chloride	106 mEq./L.		
Blood nonprotein nitrogen	20 mg./100 ml.		
Plasma cholesterol	146 mg./100 ml.		

Urine concentration test showed a maximal concentration of 1.012 after 18 hours without water.

Urine gonadotrophin ("FSH")* 0 mouse units

* The measurement of gonadotrophin was done in the laboratory of Dr. Willard Allen.

of a myocardial infarction). The laboratory data relating to endocrine function are recorded in table 1.

In the hospital the patient's diabetes mellitus was controlled on diet alone, and he showed no glycosuria. He was discharged on 12.5 mg. of cortisone once a day, 30 mg. of thyroid a day, and 10 mg. of methyltestosterone as linguets once a day. Shortly after returning home he suffered another cerebral vascular accident and died. Unfortunately, no autopsy was performed.

DISCUSSION

Although glycosuria and the requirement for exogenous insulin disappeared in this patient, hyperglycemic unresponsiveness (probably due to persisting inadequate insulin secretion) remained, as demonstrated by the diabetic glucose tolerance curve. The carbohydrate metabolism of this patient would therefore correspond to that observed by Houssay and others [14] in depancreatectomized dogs following hypophysectomy.

The diagnosis of hypopituitarism in the present patient was made on clinical evidence. The absence of cachexia does not militate against the diagnosis.[15] Adequate nutrition in the presence of hypopituitarism can be explained by the associated hypometabolism and absence of catabolic activity of the adrenal cortex.

Probably the best evidence of hypopituitarism is the absence of measurable urinary gonadotrophins. The determination was made by the method of Gorbman.[16] The normal level for a man this age would be between 10 and 20 mouse uterine units.

The diagnosis is also strengthened by the Kepler-Power-Robinson water diuresis test, which was consistent with adrenal cortical insufficiency. When the

empirical index "A" of Kepler-Power-Robinson was calculated, using urine and plasma levels of chloride and urea nitrogen, it was found to be 2.1, which is far below the accepted index for "A" of 25 or over for the normally functioning adrenal cortex. This extremely low index is perhaps supportive evidence that the delayed water diuresis is on a primary adenohypophyseal level rather than adrenal. Gaunt [18] has shown that water diuresis of rats is more impaired when the anterior lobe of the pituitary is removed than when the primary deficiency is in the adrenal cortex alone.

Sparse body and sexual hair, together with a decrease in the size of the prostate, is one of the most consistent findings in patients suffering from insufficiency of the anterior lobe of the pituitary. The normal hair and size of the prostate in this patient would therefore not be in keeping with the diagnosis. However, since he had been taking large doses of methyltestosterone for a long time it is felt that this might account for the inconsistency.

This patient may have had impairment in the function of the neurohypophysis as well as the adenohypophysis. His daily urine output was 4 to 5 liters, with maximal concentration of 1.012 and a normal nonprotein nitrogen. Diabetes insipidus, if it did exist, was mild. Destruction of the anterior lobe of the pituitary may have prevented the full diuresis of diabetes insipidus.

Without autopsy confirmation the probable pathology in the pituitary region is a matter of speculation. From the history and physical findings it would appear that more than the anterior lobe of the pituitary was involved, since weakness of the right side of the body was also present. In addition, the excessive diuresis and inability to form concentrated urine have suggested impairment of the posterior lobe of the pituitary. Harris [19] has presented evidence of hypothalamic control of the anterior lobe of the pituitary gland, mediated by way of a hypothalamic hypophyseal portal venous system. The patient's cerebral vascular accident may have involved the hypothalamus, with subsequent impairment of (1) the neural connection to the posterior lobe of the pituitary, and (2) the portal blood system to the anterior lobe, resulting in panhypopituitarism without direct involvement of the pituitary.

Summary

A case is reported of spontaneous remission of diabetes mellitus due to the development of hypopituitarism following a cerebral vascular accident. Comment is made on the various diagnostic tests and presumptive location of the lesion.

Acknowledgments

Grateful acknowledgment is made to Dr. William H. Daughaday and Dr. Bruce D. Kenamore for their kind help in the preparation of this paper.

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EDITORIAL

HEMOPHILIA AND ALLIED DISORDERS

ALTHOUGH hemophilia is a relatively rare disease, its spectacular nature and its unusual clinical and genetic features have made it a subject of unusual interest both to the laity and to the medical profession. The disease has been recognized clinically for a century, and less definitive descriptions can be found in older writings back to the Talmud. Recent studies have amplified and modified some of our conceptions of the disease.

Hemophilia is commonly defined as a disorder characterized by a tendency to abnormally persistent bleeding, eventually often exsanguinating, and by a prolonged coagulation time, which is usually hereditary, confined (almost) exclusively to males but transmitted by females as a recessive sex-linked character. The various hemorrhagic disorders can not be identified solely by the character of the bleeding. In hemophilia, however, this is most often from deep or jagged cuts or lacerations of the skin or buccal mucosa, or from dental extractions or circumcisions. Bleeding into the subcutaneous tissues, the muscles and particularly the joints is highly characteristic of the severer cases. Cutaneous ecchymoses and hematomata are common, but petechiae are rare, and epistaxis and bleeding from the lower gastrointestinal tract and uterus, although sometimes troublesome, are less common than in severe thrombocytopenia.

Of the usual clinical tests for disturbances of the coagulation factors, only the coagulation time is abnormal. The platelet count, bleeding time, clot retraction, tourniquet test, calcium, fibrinogen and prothrombin are all normal, as are also the more recently identified prothrombin-conversion accelerators. Many claims have been made that the platelets are unusually resistant or otherwise abnormal, but no convincing evidence for this has been obtained.

Brinkhous [1] showed that the immediate cause of the delayed coagulation was slow formation of thrombin and that this was associated with a very slow disappearance of prothrombin from the serum. On the basis of this observation Quick devised his test for prothrombin consumption during coagulation. When normal blood or plasma clots, the prothrombin is largely converted into thrombin, and the serum, tested under standard conditions, contains less than 20 per cent as much prothrombin as the plasma. In hemophilic serum the amount unconsumed is much greater than this, and in severe cases there may be as much as in the plasma.

Failure to consume prothrombin during coagulation is due to a deficiency of thromboplastin. The formation of active thromboplastin in the blood depends upon the interaction of (at least) two factors, one a con-

[1] Brinkhous, K. M.: A study of the clotting defect in hemophilia, the delayed formation of thrombin, Am. J. M. Sc. **198**: 509, 1935.

stituent of the plasma occurring in the globulin fraction of the proteins, and a second factor derived from the platelets.[2] It is the plasma factor which is deficient or lacking in hemophilia.

In thrombocytopenic purpura there is also reduced prothrombin consumption. Deficient formation of thromboplastin is here due to lack of the platelet factor, and if this is supplied, as in an extract of platelets, prothrombin consumption (in vitro) becomes normal in thrombocytopenic blood, but hemophilic blood is not affected. If this precaution is taken to exclude thrombocytopenia and if the presence of anticoagulants is excluded, the test has been regarded as specific for hemophilia. It has proved to be more sensitive and reliable than the coagulation time, although it may be inconclusive in the mildest cases.

Some other investigators, notably Pavlovsky[3] and Tocantins and associates,[4] attribute the disturbances in hemophilia primarily to anticoagulants. This is based in part on the observation that hemophilic blood can be made to clot like normal blood simply by diluting it adequately with physiological salt solution. It is indeed hard to understand how a deficiency of an essential substance can be compensated by further dilution, but a majority believe that anticoagulants, if present, are incidental or quite exceptional.

The plasma factor deficient in hemophilia was called the antihemophilic globulin, AHG, by Minot et al.[5] (also AHF, antihemophilic factor), and thromboplastinogen by Quick. On electrophoresis, it separates with Cohn's Fraction I, III_1 and III_2, and it has been isolated in relatively concentrated form. Such a preparation corrects the clotting defect in hemophilia in vitro and (temporarily) in vivo if an adequate amount is given.

Brinkhous and associates[6] have devised a method for estimating quantitatively the amount of AHG in blood by determining its effect on the clotting of blood from a known case of severe hemophilia. This has proved to be the most sensitive diagnostic method yet devised and has demonstrated the defect in mild cases of hemophilia whose coagulation time and prothrombin consumption were normal.

Quantitative determinations of AHG in patients with hemophilia have shown a definite correlation between the degree of the deficiency and the severity of the disease. They have shown that in a given individual there is little or no fluctuation in the quantity of this substance. Variations in the severity of the bleeding from time to time depend upon other factors,

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[3] Pavlovsky, A.: Contribution to the pathogenesis of hemophilia, Blood **2**: 185–191, 1947.

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[5] Lewis, J. H., et al.: The relation of certain globulin fractions of the plasma globulins to the coagulation defect in hemophilia, Blood **1**: 166, 1946.

[6] Langdell, R. D., Wagner, R. H., and Brinkhous, K. M.: Effect of antihemophilic factor on one stage clotting tests, J. Lab. and Clin. Med. **41**: 637, 1953.

including probably the integrity of the vascular walls. Not only is the defect constant in a given subject, but also in the various affected members of the same family, both in the same and in different generations. Genetic factors appear to determine not only the occurrence but also the severity of the defect.

The occurrence of extremely mild cases has been appreciated, and a group of such cases has been reported by Merskey.[7] Of 54 cases of known hemophilia, the coagulation time was normal in nine and only slightly prolonged in 12, remaining relatively constant in these cases over prolonged periods. Symptoms were mild or moderate in most cases and not disabling, although most had required transfusions on at least one occasion. The prothrombin consumption was moderately less than normal, and the titer of AHG, tested in at least one member of each of the eight families involved, was subnormal but not absent.

Graham, McLendon and Brinkhous [8] have reported an even milder form of the disease in a family of 79, among whom were 14 affected males. These subjects complained of easy bruising, profuse bleeding after razor cuts, tonsillectomy or dental extractions, but no hemarthrosis, and none had died of hemorrhage. The diagnosis could not be made in individual cases from the coagulation time or prothrombin consumption, but the AHG was reduced to about 20 per cent of normal. The family history indicated the usual type of recessive sex linked inheritance.

An unusual observation was the finding in four of eight (heterozygous) female carriers tested that the content of AHG in the plasma was moderately but significantly decreased. Three other women not known to be carriers showed a similar decrease. This may be a peculiarity of this one family, since the observations of the authors and most other investigators have shown no abnormality in the blood of carriers of hemophilia of average severity. There are a few exceptions. Haberman [9] reported diminished prothrombin consumption in several clinically normal females in three hemophilic families. Owren [10] reported delayed conversion of proconvertin to convertin (which requires thromboplastin) in carriers. Stefanini [11] also has stated that the blood of carriers fails to correct completely (in vitro) the clotting defect of hemophilic blood. These deviations seem rather subtle and require further confirmation. Thus far the recognition of carriers before the birth of hemophilic sons has not been dependably accomplished.

Recent studies have confirmed the generally accepted views as to the

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[10] Owren, P. A.: The diagnosis of the hemophilic conductor, in Proc. Third Internat. Congress, Internat. Soc. Hematology, New York, Grune and Stratton, 1951, p. 446.

[11] Stefanini, M.: Hemophilia: Specific entity or syndrome? Blood **9**: 273–280, 1954.

inheritance of the disease. Brinkhous and associates [12, 13] have carried out extensive studies on a strain of dogs which showed a disturbance of coagulation clinically and hematologically identical with fairly severe human hemophilia. By careful and very laborious breeding experiments they showed that the defect was transmitted as a recessive sex linked character, exactly as in the human disease. They obtained female conductors and female bleeders (hemophiliacs) under the circumstances and in the proportions which would be anticipated from the theory. The female hemophilic dogs differed in no essential from the male bleeders in the character or severity of the disease.

That hemophilia may occur in human females has also been definitely demonstrated. A typical case has been reported by Isreals et al.,[14] and Merskey [15] has restudied a family with records over seven generations in which there were four (and probably five) female bleeders. These occurred in the fifth generation, as the result of a marriage in the fourth generation of a hemophilic male and a first cousin who proved to be a conductor. The disease in this family was only moderately severe. Merskey was able to examine two of these women and found them typical hemophiliacs clinically and hematologically. They showed a moderately long coagulation time, reduced consumption of prothrombin in the serum, and their plasma did not correct the clotting defect of known hemophilic blood in vitro. Their disease did not differ in character or severity from that of the male bleeders in the family. One hemophilic woman had a hemophilic son. Quick and Hussey [16] have also reported a case in a female.

Although a family history of bleeding can be obtained from most cases of hemophilia, in some 20 to 30 per cent this is not possible. It is now generally believed that in most such cases the defect has arisen de novo as the result of a chance mutation. It has been shown mathematically that with random mating in a large general population a rare defect of this type would tend to die out and disappear after about three generations. As there appears to be no progressive change in the incidence of the disease, the frequency of such mutations must just compensate for the spontaneous disappearance of the trait. Such sporadic cases transmit the disease in the usual manner, as a sex linked recessive character, and they are typical in all other respects.

Although in typical cases of hemophilia the diagnosis can usually be made without difficulty, there are diseases due to other disturbances of co-

[12] Brinkhous, K. M., Graham, J. B., Penick, G. D., and Langdell, R. D.: Studies on canine hemophilia, Trans. of Fourth Conference on Blood Clotting and Allied Problems, New York, Josiah Macy, Jr. Foundation, 1951, p. 51.

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agulation which may simulate it. Some of such diseases have been designated as hemophilia, with or without the use of some qualifying prefix or adjective. These conditions may result from familial or congenital defects, and in severe form may show a prolonged coagulation time. Such cases may be due, e.g., to a congenital lack of prothrombin or of either of the prothrombin conversion accelerators. A definite diagnosis may require a precise and detailed estimation of many different factors, possible only in a large medical center.

One procedure which has been much used is to test the effect of the plasma of the case under study on the clotting time of the blood of a patient whose disease is known, e.g., a case of typical hemophilia. Although there are some pitfalls, if the defect of coagulation of the hemophilic blood is not remedied, the patient under study presumably has hemophilia also. If the coagulation is restored virtually to normal, the bleeding in the patient must be due to some other defect, since his blood evidently contains the factor lacking in the hemophilic blood. Aggeler et al.[17] applied this test to a study of the blood of a boy with supposed hemophilia and found that his plasma corrected the coagulation defect of blood from a known hemophiliac, and vice versa. The defect was attributed to lack of a precursor of thromboplastin in the plasma which is different from the AHG lacking in ordinary hemophilia. This they termed "plasma thromboplastin component," PTC.

Mutual correction of the clotting defects by mixing bloods from two supposed hemophiliacs had previously been reported by Pavlovsky, in 1947,[8] who attributed the effect to neutralization of anti-coagulants. Similar observations were reported by Koller et al.[18] who found that 10 of 19 cases so studied (in Switzerland) were classical hemophilia, but nine showed a lack of a different substance which he called Factor IX.

Observations essentially identical with Aggeler's were made independently in Great Britain by Biggs et al.,[19] who identified seven such cases. They termed the disease "Christmas disease" and the deficient substance "Christmas factor" from the name of the first patient observed. Further confirmatory reports have appeared, both in this country and in Great Britain. There is no doubt that this Christmas factor is identical with Aggeler's PTC. Studies by these various investigators have shown that the factor PTC is quite different from AHG. It is found in Cohn's fraction III and IV (instead of I and III_1), it is precipitated by 40 to 50 per cent ammonium sulfate (instead of 33 per cent), and it is adsorbed by barium sulfate and removed by a Seitz filter, whereas AHG is not. On the other hand, unlike AHG, it is stable on storage, it is not consumed during co-

[17] White, S. G., Aggeler, P. M., and Glendenning, M. B.: Plasma thromboplastin component (PTC). A hitherto unrecognized blood coagulation factor. Case report of PTC deficiency, Blood **8**: 101–124, 1953.

[18] Koller, F., et al.: Ueber eine besondere Form haemorrhagischer Diathese, Schweiz. med. Wchnschr. **80**: 41, 1950.

[19] Biggs, R., et al.: Christmas disease. A condition previously mistaken for haemophilia, Brit. M. J. **2**: 1378–1382, 1952.

agulation, and it is abundant in serum. Biggs' observations indicate that the defect is inherited as a recessive sex linked character, like AHG, but evidently in a different locus on the X chromosome. Clinically the disease is identical with hemophilia. In this country and in Great Britain its frequency is about one fifth as great.

More recently Rosenthal et al.[20] have reported several cases of a relatively mild hemorrhagic disease resembling hemophilia, in which there is a deficiency of a third plasma factor, termed by them "plasma thromboplastin antecedent" (PTA). This can be differentiated from the other two factors by suitable physical and chemical tests. This disturbance affects both males and females and is probably transmitted as a dominant trait.

Finally, Aggeler has stated [21] that he has evidence, not yet entirely conclusive, of a coagulation disturbance due to lack of a fourth prothromboplastic plasma factor.

Patients with a deficiency of either PTC or PTA respond well to transfusions of stored plasma or serum as well as fresh plasma, but *not* to purified AHG. The benefit may last for seven to 10 days. Classical hemophilia responds only to large amounts of *fresh* plasma or concentrated AHG, the response is often less satisfactory, and the benefit is brief, 48 to 72 hours. From the practical standpoint, it is important to use *fresh* plasma in all cases or to make a precise diagnosis of classical hemophilia before administering AHG.

What, then, is hemophilia, and what term shall be applied to these variant disorders? To answer this question the editor of Blood arranged a symposium in the March number, in which eight authors or groups who have been working in the field have participated. As might be anticipated eight different suggestions have been offered. To attempt a discussion of them here would only add to the confusion. Until an amicable agreement has been reached by these investigators, the writer would prefer to cling to the familiar term hemophilia, at least for the "classical" form of the disease. The variants, when recognized, may be designated by a qualifying term to indicate the factor which is deficient.

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[20] Rosenthal, R. L., Dreskin, O. H., and Rosenthal, N.: New hemophilia-like disease caused by deficiency of a third thromboplastin factor, Proc. Soc. Exper. Biol. and Med. **82**: 171, 1953.

[21] Aggeler, P. M., White, S. G., and Spaet, T. H.: Deuterohemophilia: Plasma thromboplastic factor B deficiency. Plasma thromboplastin component (PTC) deficiency. Christmas disease, Hemophilia B, Blood **9**: 246-253, 1954.

DIAGNOSES OF THE CASES DISCUSSED AT CLINICAL-PATHOLOGICAL CONFERENCES AT THE THIRTY-FIFTH ANNUAL SESSION, CHICAGO, APRIL, 1954

Tuesday.

Case 1.

Sarcoidosis with involvement of the heart.

Case 2.

Scleroderma.

Wednesday.

Case 1.

Cryptococcus (torular) meningitis.

Case 2.

Diffusely infiltrative carcinoma of the stomach with generalized metastases.

Thursday.

Focal papillary carcinoma (obstructive) of the hepatic ducts at the hilum of the liver.

Friday.

Case 1.

Essential thrombocytopenic purpura with chronic peptic ulcer of the stomach with carcinomatous degeneration.

Case 2.

Primary amyloidosis of the heart, kidneys and other viscera.

REVIEWS

The Heart Beat: Graphic Methods in the Study of the Cardiac Patient. By ALDO A. LUISADA, M.D., Associate Professor of Medicine and Director, Division of Cardiology, The Chicago Medical School, under a Teaching Grant of the National Heart Institute, U. S. Public Health Service. 527 pages; 18 × 26 cm. Paul B. Hoeber, Inc., New York, N. Y. 1953. Price, $12.00.

Many technics are employed for analyzing cardiac action, and these methods have become increasingly widespread and complex. It is the purpose of this book to ". . . correlate a great mass of data and to present them with a unified concept." The author discusses the technic and interpretation of normal tracings, the physiologic variants of the graphic tracings, and the clinical application of graphic methods. These three divisions are preceded by a description of cardiovascular dynamics and electrophysiology and followed by an appendix describing several types of apparatus. Included are sections devoted to phonocardiography, cardiography, ballistocardiograms, jugular and hepatic tracings, intrathoracic tracings, arterial pulsations, pressure tracings, roentgen and electrokymography, respiratory tracings, and tracings of electrical phenomena of the heart and vessels.

The author presents the history, technic, analysis, and conclusions concerning each technic, and there is a bibliography after each chapter. The book is well edited and the index carefully prepared. Many of the tables are extremely valuable. It is difficult to cover adequately within one volume the tremendous field which the author has attempted. Of necessity, some subjects are stressed and others only outlined briefly. The contents are so broad in scope that it is not surprising to have differences in opinion as to interpretation and evaluation. This book does serve the useful purpose of containing within one volume graphic technics employed in the study of the cardiac patient and should prove a useful text for this purpose.

L. S.

Group Psychotherapy: Studies in Methodology of Research and Therapy. Report of a Group Psychotherapy Research Project of the U. S. Veterans Administration. By FLORENCE B. POWDERMAKER, Ph.D., M.D., Responsible Investigator; JEROME D. FRANK, Ph.D., M.D., Principal Assistant; in collaboration with JOSEPH ABRAHAMS, M.D., ALBERT E. DREYFUS, M.D., HENRY S. MAAS, Ph.D., ROBERT MACGREGOR, M.A., JOSEPH B. MARGOLIN, M.A., HELEN T. NASH, B.A., MORRIS B. PARLOFF, M.A., DAVID ROSENTHAL, Ph.D., and EDITH VARON, M.A., M.S. 615 pages; 16 × 24 cm. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. 1953. Price, $6.50.

Although this book will be of most interest to psychiatrists, psychologists and social workers who work in psychiatric hospitals and clinics, it is not intended merely as a guide or hand-book for those engaged in group therapy. The authors are here reporting on a carefully conducted research project designed to study the various elements that go into success and failure with the methods of group therapy. These methods were studied as they were applied to two groups of patients under the care of the Veterans Administration. The first group comprised ambulatory patients, largely psychoneurotic, who were treated in an out-patient Mental Hygiene Clinic. The second group consisted of schizophrenic patients in a mental hospital.

The findings and conclusions can not be adequately covered in a review. However, this study agreed with most studies of group therapy in stressing that this method is able to help some patients who can not be, or have not been, helped by individual psychotherapy. Many patients can be helped by it alone while others benefit by receiving both individual and group therapy. Again like others, this study demonstrates that group therapy does not cut down on the time spent on patients, or enlarge the numbers that can be taken care of by a limited supply of therapists. It has a value all its own and, as a method of therapy, it has so adequately demonstrated its value that no psychiatric clinic or hospital should neglect this method. It is important for all who plan to engage in this type of work to read this book.

H. W. N.

The Anatomy of the Nervous System: Its Development and Function. 9th Ed. By Stephen Walter Ranson, M.D., Ph.D., Late Professor of Neurology and Director of Neurological Institute, Northwestern University Medical School, Chicago; revised by Sam Lillard Clark, M.D., Ph.D., Professor of Anatomy, The Vanderbilt University School of Medicine, Nashville. 581 pages; 17 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1953. Price, $8.50.

The first edition of this book in 1920 was an excellent text of neuro-anatomy. It has been continuously improved by conservative revision every fourth year since that time. It stands today as one of the best textbooks in the field of neuro-anatomy. The account of the structure of the nervous system has been blended with functional considerations in a skillful and concise way. For example, there is a chapter on clinical illustrations which, in the former edition, contained twelve well chosen cases to illustrate to the student the possible practical value of knowing neuro-anatomy. In this ninth edition, two additional very interesting and appropriate case histories have been described. In all of these case presentations, a sufficient number of questions is included to require the student to think and analyze the case as he reads. An atlas on sections of the brain stem has always been a very good feature of this book.

In spite of all the excellent qualities of the book, it (like all the other first class texts in neuro-anatomy which are available today) lacks a practical comprehensive set of directions for the dissection of the human brain, and the addition of this would greatly improve the book. It is true that there is a set of directions for the dissection of the head of the dogfish and the brain of a fetal pig, but the outline for the laboratory study of the human central nervous system contains a very inadequate set of directions for dissecting a human brain.

The recent advances in neuro-anatomy and neuro-physiology, that have come from many investigators using various disciplines, have been incorporated in this edition in the usual conservative manner. In particular, the inhibitory and facilitory mechanisms in the brain stem and recent knowledge concerning the part which the cerebellum plays have been summarized to increase appreciation of the manner in which neurological mechanisms are integrated.

The work of Penfield and his associates has been reviewed and added to the chapters on the cerebral cortex. His observations in the realm of memory and speech and other functions peculiar to man (studied on human subjects under local anesthesia) have been added to the text in appropriate places. There are a number of new illustrations, some in color. This ninth revision of Ranson-Clark's Neuro-Anatomy may be highly recommended as a text for medical students and as a reference book for practicing physicians.

F. H. J. F.

An Atlas of Skull Roentgenograms. By BERNARD S. EPSTEIN, M.D., Associate Radiologist, The Jewish Hospital of Brooklyn, Brooklyn, New York, and LEO M. DAVIDOFF, M.D., Neurosurgeon to the Mount Sinai Hospital, New York City and Director of Neurological Surgery, The Beth Israel Hospital, New York City. 415 pages; 18 × 26 cm. Lea & Febiger, Philadelphia 6, Pa. 1953. Price, $15.00.

This book is truly an atlas consisting mainly of 603 illustrations. The text has been kept at a minimum with much of the descriptive material contained in the legends accompanying the illustrations. The minimum reading material with each disease contains only the basic diagnostic and etiological points.

Throughout this atlas, the emphasis is mainly on the routine skull roentgenogram but laminagraphy is stressed to bring out certain details. An occasional pneumoencephalographic film is included to prove a point or to illustrate better the site or extent of a disease process. Each important diagnostic point, including atypical as well as classical changes, has been illustrated.

In general the roentgenographic reproductions are excellent with no attempt to retouch them. The obvious changes are described in the legends. Where the changes are not immediately visible to the reader and where it is important to indicate finer detail arrows are used.

The completeness of this book is demonstrated in the first chapter where the authors discuss and illustrate the normal skull and all its normal variations from birth through adult life. They have performed an excellent task in covering skull roentgenography so completely, and this atlas will be especially beneficial to radiologists, neurologists and neuro-surgeons.

J. M. D.

Clinical Electrocardiography in Children. By GERTRUDE H. B. NICOLSON, M.D., Associate in Cardiology and Chief of Children's Cardiac Clinic at St. Luke's Hospital, Instructor in Pediatrics at Columbia University. 118 pages; 14 × 21.5 cm. The Macmillan Company, New York. 1953. Price, $3.25.

This volume is based upon the study of electrocardiograms taken on 500 children, with the child in a sitting or propped-up position. There are brief discussions of the electrocardiogram in the normal child, of heart position, bipolar and unipolar limb leads, unipolar precordial leads, the child's electrocardiogram in disease, and the electrocardiogram in congenital heart disease. There are 58 figures and a number of tables. The author assumes some familiarity with basic electrocardiographic principles on the part of the reader. The organization of the volume does not seem good, and impresses the reviewer as being concerned too little with perspective, while at the same time needed details are omitted. There are a number of inaccuracies and omissions.

This text is small, but neither adequate nor comprehensive enough to supply the need for a good volume on the subject of clinical electrocardiography in children.

S. S.

Essentials of Infant Feeding for Physicians. By HERBERT FREDERIC MEYER, A.B., M.D. 252 pages; 15.5 × 23.5 cm. Charles C. Thomas, Springfield, Ill. 1952. Price, $6.75.

This book presents the practical considerations of feeding of infants. The main scientific background of infant feeding is summarized, and current trends, such as self-demand feeding, are discussed. Common and proprietary foods, such as milk prepara-

tions, carbohydrate and vitamin supplements and solid foods, are considered. The data and discussions of commercial preparations are useful in helping the physician organize the essential facts of those items stripped of folk lore and advertising claims. Various nursery routines are appended.

The book is written in a personalized style which makes for easy reading.

G. E. G.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Acute Renal Failure. Publication Number 192, American Lecture Series. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P., Professor and Chairman, Department of Experimental Medicine, Lecturer in Pharmacology and Toxicology, Southwestern Medical School of the University of Texas, etc. Edited by ROSCOE L. PULLEN, M.D., F.A.C.P., Professor of Medicine and Dean, University of Missouri School of Medicine, Columbia, Missouri, etc. 92 pages; 22.5 × 14.5 cm. 1954. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $4.00.

The Biochemistry of Clinical Medicine. By WILLIAM S. HOFFMAN, Ph.D., M.D., Professorial Lecturer in Medicine, University of Illinois College of Medicine, etc. 681 pages; 25 × 16 cm. 1954. The Year Book Publishers, Inc., Chicago. Price, $12.00.

Digital Plethysmography: Introducing a Method for Recording Simultaneously the Time Course of the Rate of Blood Flow Into and Out of the Finger Tip. Modern Medical Monographs 11. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, etc. 134 pages; 22 × 14 cm. 1954. Grune & Stratton, New York. Price, $5.00.

Diseases of the Liver. By MITCHELL A. SPELLBERG, M.D., F.A.C.P., Associate Professor of Clinical Medicine, University of Illinois School of Medicine, etc. 646 pages; 28 × 20 cm. 1954. Grune & Stratton, New York. Price, $16.50.

Electrocardiography. By E. GREY DIMOND, M.D., Professor and Chairman, Department of Medicine, Director, Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City, Kansas. 261 pages; 28.5 × 21.5 cm. 1954. The C. V. Mosby Company, St. Louis. Price, $14.00.

The Exteriorization of the Mental Body: A Scientific Interpretation of the Out-of-the-Body Experience Known as Pneumakinesis. By JAMES BAKER, JR. 32 pages; 21.5 × 14 cm. (paper-bound). 1954. The William-Frederick Press, New York. Price, $1.50.

French's Index of Differential Diagnosis. 7th Ed. Edited by ARTHUR H. DOUTHWAITE, M.D., F.R.C.P., Senior Physician, Guy's Hospital, etc. 1,046 pages; 25.5 × 16.5 cm. 1954. The Williams and Wilkins Company, Baltimore. Price, $20.00.

Fundamentals of Neuropathology. By WILLIAM BROOKS DUBLIN, M.D., Chief, Laboratory Service, Veterans Administration Hospital, Denver, Colorado, etc. 685 pages; 26 × 17.5 cm. 1954. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $18.50.

Psychophysiologic Medicine. By EUGENE ZISKIND, M.D., Clinical Professor of Psychiatry, University of Southern California School of Medicine, etc.; foreword by JOHN C. WHITEHORN, M.D., Henry Phipps Professor of Psychiatry, The Johns Hopkins University, etc. 370 pages; 24 × 15.5 cm. 1954. Lea & Febiger, Philadelphia. Price, $7.00.

Roentgenographic Technique: A Manual for Physicians, Students and Technicians. 4th Ed. By DARMON ARTELLE RHINEHART, A.M., M.D., F.A.C.R., Emeritus Professor of Anatomy and Roentgenology, University of Arkansas, etc. 454 pages; 24 × 15.5 cm. 1954. Lea & Febiger, Philadelphia. Price, $8.50.

The Science Book of Wonder Drugs. By DONALD G. COOLEY; illustrated by WILLIAM DRAUT. 247 pages; 20 × 14.5 cm. 1954. Franklin Watts, Inc., New York. Price, $2.95.

Symposium on Protein Metabolism: Proceedings of the Nutrition Symposium Held at the University of Toronto, Toronto, Ontario, Canada, October 30, 1953. Nutrition Symposium Series Number 8. By A. E. AXELROD, J. R. BEATON, PAUL R. CANNON, BACON F. CHOW, LAURENCE E. FRAZIER, OLIVER H. GAEBLER, RANDOLPH H. HUGHES, RUTH M. LEVERTON, HERBERT POLLACK and J. PRUZANSKY. 107 pages; 23 × 15.5 cm. (paper-bound). 1954. The National Vitamin Foundation, Incorporated, New York. Price, $1.50.

COLLEGE NEWS NOTES

Summary Report on the 35th Annual Session of the College

The 35th Annual Session of the American College of Physicians, held at the Conrad Hilton Hotel, Chicago, under the Presidency of Dr. LeRoy H. Sloan and the General Chairmanship of Dr. Howard Wakefield, was the second largest meeting in gross registration in the history of the College, being exceeded only by the 1949 Annual Session in New York City. In point of member registration, it was the third largest meeting, being excelled both by New York in 1949 and by Atlantic City in 1953. Comparable figures on the three meetings are as follows:

		Members	Guest Physicians	Guest Non-Physicians	Students	Exhibitors	Ladies	Total
Chicago	(1954)	2,233	1,517	27	183	623	803	5,386
Atlantic City	(1953)	2,316	1,057	43	15	484	1,063	4,978
New York	(1949)	2,486	1,471	38		665	967	5,627

From the standpoint of the reception of the program by the registrants, the Chicago meeting was second to none. The program was more extensive than customary; General Sessions were split into two or more sections, because of room facilities; the Morning Lectures were expanded; Panel Discussions and Clinical-Pathological Conferences were diversified; the Colored Television Clinics were improved, and Hospital Clinics were resumed. It is to be regretted that some attendants were disappointed in being unable to obtain seating facilities in some of the more popular Panels and Lectures. It is significant that in practically every case, rooms accommodating the Clinical-Pathological Conferences were filled to overflowing, thus revealing the ever-increasing popularity of this type of program, as organized by the College. Contrary to usual experience, the attendance at the Convocation for the induction of new members was large, numbering about 1,800 individuals. The multiplicity of social events, along with a very crowded program, is believed to be responsible for the small attendance at the Annual College Banquet, an affair that was conducted with superior technique and true attraction—a Banquet that actually transcended any held by the College in many years.

The resumption of Hospital Clinics on two mornings of the Convention were observed with rather keen interest. Daily attendance at the Clinics averaged 1,050; seven of the Clinics were filled to capacity, but several were not particularly well attended; this probably did not represent a sign of lack of interest in the Clinics, but rather a preference for certain other competing programs which were available without leaving the headquarters.

The Technical Exhibit was the largest in the history of the College, occupying 138 booths, with 109 firms or agencies participating. Guest physicians were in attendance, outside the United States and Canada, from Cuba, Mexico, Egypt, England, India, New Zealand, South Africa, Sweden and Venezuela. Sir W. Russell Brain, President of the Royal College of Physicians of London, appeared on the program of General Sessions and Morning Lectures and at the Annual Convocation presented to the College a replica of the ancient Caduceus of the Royal College of Physicians of London, one of the insignia of office of their President. The replica was accom-

panied by a formal Scroll, signed by the President and Registrar of the Royal College. Another special guest was Dr. U. S. von Euler, of Stockholm, Sweden, who delivered the Lilly Lecture, "Physiological Basis for the Clinical Use of Nor-Adrenaline." The College conferred Honorary Fellowships on both Sir W. Russell Brain and Dr. U. S. von Euler.

The John Phillips Memorial Medal for 1954 was awarded to Donald D. Van Slyke, Ph.D., Sc.D., M.D., of the Brookhaven National Laboratory, Upton, N. Y., and the James D. Bruce Memorial Medal for 1954 in Preventive Medicine was awarded to David Marine, A.M., M.D., D.Sc., Rehoboth, Del. (formerly of New York City). The Alfred Stengel Memorial Award was made to Dr. Thomas M. McMillan, Philadelphia, in recognition particularly of his services to the College through its postgraduate program and of his eminence as an internist and cardiologist.

Masterships were conferred upon Doctors Walter L. Bierring, Des Moines, Robert A. Cooke, New York, Egerton L. Crispin, Los Angeles, and Hugh J. Morgan, Nashville.

The names of new Associates and new Fellows elected during the Chicago Session have already appeared in the May, 1954, issue of this Journal. Dr. Cyrus C. Sturgis, Professor of Medicine and Head of the Department of Medicine, University of Michigan Medical School, Ann Arbor, was inducted as President for 1954–55; Dr. George F. Strong, Clinical Professor of Medicine, University of British Columbia Faculty of Medicine, Vancouver, B. C., was made President-Elect; Dr. Marion A. Blankenhorn, Cincinnati, Ohio, Dr. George H. Lathrope, Morristown, N. J., and Dr. Ramon M. Suarez, San Juan, P. R., were elected, respectively, First, Second and Third Vice Presidents. Dr. Asa L. Lincoln, New York, Dr. Walter L. Palmer, Chicago, and Dr. Wallace M. Yater, Washington, were reëlected to the Board of Regents; Dr. Fuller B. Bailey, Salt Lake City, Dr. J. Murray Kinsman, Louisville, and Dr. Karver L. Puestow, Madison, were elected as new members of the Board of Regents. Among new members of the Board of Governors elected at Chicago are: Dr. Rudolph H. Kampmeier, Nashville, Governor for Tennessee; Dr. Theodore C. Bauerlein, Salt Lake City, Governor for Utah; Dr. Marion D. Hargrove, Shreveport, Governor for Louisiana; Dr. D. O. Wright, Birmingham, Governor for Alabama; Dr. Sam A. Overstreet, Louisville, Governor for Kentucky; Dr. Frederick W. Madison, Milwaukee, Governor for Wisconsin; Dr. Percy H. Sprague, Edmonton, Governor for Alberta. Full personnel of Officers, Regents and Governors was published in the May, 1954, issue of this Journal. The personnel of Committees is published elsewhere in this issue.

At the conclusion of the Annual Session in Chicago, a representative group of members of the College and members of their families, numbering 65, participated in a Post-Convention Tour to Mexico, where a scientific program of Seminars in Medicine was conducted at the Instituto Nacional de Cardiologia and the Hospital de Enfermedades de la Nutricion, in the form of a postgraduate course. Dr. Ignacio Chavez, College Governor for Mexico, and Dr. Salvador Zubiran, F.A.C.P., were in charge, and they and the Fellows of the College of Mexico extended many courtesies and privileges to the group.

The 1955 Annual Session will be held at Philadelphia, April 25–29, under the Presidency of Dr. Cyrus C. Sturgis, Ann Arbor, and the General Chairmanship of Dr. Thomas M. Durant, Philadelphia.

The 1956 Annual Session will be held at Los Angeles, Calif., April 16–20, under the Presidency of Dr. George F. Strong, Vancouver, B. C., and the General Chairmanship of Dr. George C. Griffith, Los Angeles.

Auditor's Report, Year Ending Dec. 31, 1953

February 20, 1954

To the Board of Regents

American College of Physicians, Inc.
4200 Pine Street
Philadelphia 4, Pa.

Dear Sirs:

I have examined the accounts of the

American College of Physicians, Inc.

for the year ending December 31, 1953, and the accompanying statements, including the Balance Sheet at December 31, 1953, the analyses of the General Fund and the Endowment Fund and the Statement of Income Account for the calendar year 1953 are in accordance with the books of Account, and in my opinion present fairly the financial position at December 31, 1953 and the results of operations for the calendar year 1953, in conformity with generally accepted accounting principles applied on a basis consistent with that of preceding years, and subject to the following comments:

Cash: The cash was properly accounted for, was confirmed by direct correspondence with the following depositories, and the Petty Cash verified:

Girard Trust Corn Exchange Bank, Philadelphia	$46,564.98
Provident Trust Company, Philadelphia	29,052.77
Royal Bank of Canada, Montreal	760.50
Petty Cash	250.00
	$76,628.25

Accounts Receivable: The Accounts Receivable were examined and found to be less than one year old and appear to be collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were accounted for by direct correspondence and the income for the period under review was verified. The investment transactions are recorded properly in the general books of account and in the Investment Ledger, which is in agreement with the investment accounts of the General Ledger.

General: The changes in the amount of the ENDOWMENT FUND and the GENERAL FUND during the year 1953 are as follows:

	Balance Jan. 1, 1953	Balance Dec. 31, 1953	Increase
Endowment Fund	$382,598.64	$ 412,321.25	$ 29,722.61
James D. Bruce Fund	10,000.00	10,000.00	
A. Blaine Brower Fund	20,000.00	20,000.00	
General Fund	576,555.52	660,149.32	83,593.80
Restricted Funds	1,288.82	1,426.72	137.90
	$990,442.98	$1,103,897.29	$113,454.31

The Executive Secretary has analyzed the income of the ANNALS OF INTERNAL MEDICINE according to Volume, so that the income and expenses are stated according to the year of publication, with the exception of Volumes of prior years, which are closed out and not carried in an inventory account, with the sales properly credited to the General Fund according to the date of sale.

General Comments: The prepaid insurance at December 31, 1953 was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the Furniture and Equipment Accounts represent proper additions to the account, and the allowances for depreciation appear to be adequate. A depreciation reserve account has been set up for the Headquarters Building in accordance with the action of the Board of Regents at the meeting of December 12, 1937, which provided that depreciation on the Building should be taken into account at the rate of $1,000.00 per year and increased in 1949 to $2,000.00. The footings and extensions of the inventory were verified.

All ascertainable liabilities have been included in the Balance Sheet.

All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in banks and all disbursements, as indicated on the vouchers, cancelled checks and bank statements were properly recorded in the books of account.

Respectfully submitted,

(Signed) DAVID ROBINOVITZ, *Auditor*

American College of Physicians, Inc.

Balance Sheet, December 31, 1953

General Fund

Assets		
Current:		
Cash in Banks and on Hand		$ 70,036.67
Accounts Receivable		13,085.77
American Air Lines		425.00
Inventory of Keys, Pledges and Frames		362.15
Accrued Income on Endowment Fund Investments		2,528.34
Accrued Income on General Fund Investments		1,557.38
Investments at Book Value		526,375.67
Insurance Deposit		555.00
Total Current Assets		$614,925.98
Deferred:		
Expenses, 35th Annual Session	$ 6,791.06	
1953 Directory	2,700.95	
Advertising, Volume XL	4.84	9,496.85
Fixed:		
College Headquarters:		
Real Estate	112,882.32	
Less Depreciation	22,000.00	90,882.32
Furniture and Equipment, at cost	22,636.44	
Less Depreciation	8,093.23	14,543.21
Investment, Real Estate, 404–12 S. 42nd St.		9,647.72
		$739,496.08

Liabilities		
Accounts Payable		$ 87.37
Miscellaneous		2,125.85
Deferred Income:		
Advance Subscriptions, Annals of Internal Medicine, Volumes XL to XLVII		62,087.27
1954 Exhibits, paid in advance		2,458.26
RESTRICTED FUNDS:		
Income on James D. Bruce Fund Investments		488.12
Income on A. Blaine Brower Fund Investments		938.60
Reserve, Research Fellowship Fund:		
E. H. Estes, Jr. (1952–53)	$ 661.29	
S. H. Ingbar (1952–53)	1,750.00	
Reserve, 1952–53	8,750.00	11,161.29
Total Current Liabilities & Funds		$ 79,346.76
General Fund, as annexed		660,149.32
		$739,496.08

Endowment Fund

Assets	
Current:	
Cash	$ 6,591.58
Investments at Book Value	435,729.67
Accrued Income on Investments	2,528.34
	$444,849.59

Liabilities	
Current:	
Endowment Fund, Principal	$412,321.25
Accrued Income, Due to General Fund	2,528.34
James D. Bruce Fund	10,000.00
A. Blaine Brower Fund	20,000.00
	$444,849.59

Summary of Operations, General Fund, for the Calendar Year 1953

Income:			
Annual Dues		$ 55,441.18	
Initiation Fees		13,065.00	
Subscriptions, ANNALS OF INTERNAL MEDICINE		139,211.59	
Advertising, ANNALS OF INTERNAL MEDICINE		63,266.28	
Income from Investments, General Fund (including Accrued)		25,133.69	
Income from Investments, Endowment Fund (including Accrued)		17,213.56	
Dividend on Perpetual Insurance Deposit		60.00	
1951 Directory Sales		36.05	
Postgraduate Courses, Balance		3,641.00	
Profit on Sale or Maturity of Securities, General Fund		224.69	
Thirty-fourth Annual Session:			
Exhibits	$ 39,145.15		
Guest Fees	6,651.00	45,796.15	
TOTAL INCOME			$363,089.19
Expenses:			
Salaries		$ 71,882.62	
Communications		11,303.86	
Office Supplies and Stationery		4,426.65	
Printing		104,372.50	
Traveling Expenses		13,152.79	
Maintenance		124.82	
Miscellaneous		1,752.36	
College Headquarters—Maintenance, Taxes, Insurance, etc.		5,761.30	
Depreciation on College Headquarters Building		2,000.00	
Depreciation on Furniture and Equipment		2,251.64	
Keys, Pledges and Frames		252.80	
Regional Meetings		6,840.13	
John Phillips Memorial Award		359.62	
Investment Counsel Service and Security Custodian's Fee		1,163.00	
Employees' Pension Fund		6,227.60	
Bad Debts		57.50	
Advertising Discount		1,362.09	
Loss on Sale or Maturity of Securities, General Fund		11.30	
Joint Commission on Accreditation of Hospitals		10,489.05	
Collection and Exchange		24.66	
Thirty-fourth Annual Session—Special Expenses:			
Committee on Panels	$ 537.41		
Committee on Publicity	745.07		
Committee on Ladies' Entertainment	1,229.16		
Convocation	1,680.37		
Regents-Governors Dinner	1,365.16		
Registration	325.61		
Television Program	1,734.05		
Rent	3,743.39		
Other Miscellaneous	3,756.32		
Divertissement Program	3,501.90		
Banquet Deficit	292.56		
College Booth Expenses	117.50		
Butterworth Exhibit	576.65		
Clinical Pathological Conferences	5.00		
Schering Corp. (General Chmn's Dinner)	187.50	19,797.65	
Forwarded		$263,613.94	$363,089.19

Income, Brought Forward			$363,089.19
Expenses, Brought Forward		$263,613.94	
404–12 S. 42nd Street:			
Maintenance	$ 1,064.00		
Heat, Light, Gas and Water	53.64		
Taxes	515.10		
Insurance	94.14		
	$ 1,726.88		
Rent Received	1,650.00		
Excess of Expenses over Rent		76.88	
TOTAL EXPENSES			$263,690.82
Net Income for 1953 Credited to General Fund			$ 99,398.37

GIFTS TO COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College is indeed grateful to the following members who have presented copies of their books to the College Library of Publications by Members:

Dr. Samuel Bellet, F.A.C.P., Philadelphia—*Clinical Disorders of the Heart Beat*

Dr. Joseph I. Goodman, F.A.C.P., Cleveland—*The Diabetic Neuropathies,* with Drs. Sigfried Baumoel, Leonard Frankel, Louis J. Marcus and Sigmund Wassermann

Dr. S. S. Lichtman, F.A.C.P., New York City—*Diseases of the Liver, Gallbladder and Bile Ducts*

Dr. John E. Deitrick, F.A.C.P., Philadelphia—*Medical Schools in the United States at Mid-Century,* with Dr. Robert C. Berson

Dr. William A. Brams, F.A.C.P., Chicago—*Managing Your Coronary*

Dr. Jack C. Norris, F.A.C.P., Atlanta, Ga.—*Gleanings From a Doctor's Eye*

Dr. Emanuel Goldberger, F.A.C.P., New York City—*Unipolar Lead Electrocardiography and Vectorcardiography* (3rd edition)

Dr. William S. Middleton, M.A.C.P., Madison, Wis.—*Physiological Methods in Clinical Practice*

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College, and thus the Library has become a living memorial to the member-authors.

MEETINGS, A.C.P. COMMITTEE ON CREDENTIALS

The following meetings of the Committee on Credentials of the American College of Physicians have recently been scheduled; they will all be held in Philadelphia on the dates indicated:

November 12–13, 1954
March 19–20, 1955
April 23, 1955

Proposals for action at the above meetings must be received at College Headquarters sixty days in advance of these dates. Governors may require that proposals be in their hands ninety days before the meetings.

A.C.P. PROFESSIONAL LIABILITY INSURANCE

A general report of the progress of our Professional Liability (Malpractice) Group Insurance Plan was given to the members during the Annual Session in Chi-

cago. This report revealed the fact that about 1,000 members are now insured in this Plan. The number is increasing from month to month, as policies previously held by members come up for renewal.

In most areas rates under the College Plan are considerably less than currently quoted renewal premiums on individual policies—in some areas as much as 50% less. As the Plan grows and our experience remains satisfactory, the rates will gradually be reduced. In order to accomplish this result, we must have the active assistance of the members as evidenced by their participation in the Plan. Participation of members not now insured will be advantageous to the Plan as a whole and to members individually. The present Plan has been in effect almost a year and a half, but not one claim has yet been received. History is proving the College group to be a preferred risk. The administration of the Professional Liability Plan has been moved to the Association Service Office, 318 Delaware Trust Bldg., Wilmington, Del. In the future all requests for information, payment of premiums and any other matter in connection with this Plan should be addressed to that office. In case of an emergency, call that office by telephone, Wilmington 8–1662. This does not affect the administration office of the Health and Accident Plan, which remains at 1500 Walnut St., Philadelphia 2, Pa., the Philadelphia address of the Association Service Office.

The College agents urge you when your individual policy expires to send your application for Professional Liability coverage in the College Plan.

Dr. Kenneth B. Babcock, Detroit, Succeeds Dr. Edwin L. Crosby as Director of the Joint Commission on Accreditation of Hospitals

On April 15, it was announced that Dr. Kenneth B. Babcock of Detroit had been appointed Director of the Joint Commission on Accreditation of Hospitals to succeed Dr. Edwin L. Crosby, who has become Executive Director of the American Hospital Association.

The Joint Commission is an independent group voluntarily supported by five medical agencies in the United States and Canada, namely, the American College of Physicians, the American College of Surgeons, the American Hospital Association, the American Medical Association and the Canadian Medical Association. It was organized in 1951 to take over the hospital accrediting program from the American College of Surgeons, which had conducted the program since 1918. The new Joint Commission last year fully accredited 2,920 hospitals and gave provisional accreditation to 498 hospitals.

The American College of Physicians provides one full-time inspector, Dr. John Hinman, for inspection of the departments of medicine.

Dr. Babcock is a graduate (1926) of the University of Michigan Medical School, a Fellow of the American College of Surgeons and of the American College of Hospital Administrators. He has been Director of the Grace Hospital, Detroit, since 1947. He has been President of the Michigan Hospital Service (Blue Cross) for 3 years, and a member of the Board of Directors of the Michigan Medical Service (Blue Shield).

Directory of Professional Motion Picture Films and Authors

The forthcoming *Directory of Professional Motion Picture Films and Authors* enables officials of state and other societies, university faculties, program chairmen, hospitals, film authors and other eminent educators to locate, evaluate and procure a suitable film with a minimum of time and effort.

To assure the listing of all outstanding professional 16 mm. films—regardless of availability—in the forthcoming *Directory of Professional Motion Picture Films and*

Authors now being compiled, all film authors are urgently requested to write immediately for film questionnaires. Other members of the profession are invited to cooperate in this endeavor by forwarding this announcement to an author or by directly providing the film title and name and address of any film author. Please send your valuable information to: Professional Publications, Compilation Department, 2010 Kentucky Street, Lawrence, Kans.

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital by Louis N. Katz, M.D. (Director of the Cardiovascular Department, Medical Research Institute) and associates. The class will meet daily from 9:00 a.m. to 5:00 p.m., August 2 through August 14.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

Drs. Howard B. Sprague and Robert L. King Honored by A.H.A.

Drs. Howard B. Sprague, F.A.C.P., Boston, and Robert L. King, F.A.C.P., Seattle, Wash., were the respective recipients of a Gold Heart Award and the Distinguished Service Silver Medallion of the American Heart Association during the annual meeting in Chicago. Dr. E. Cowles Andrus, F.A.C.P., Baltimore, newly installed President, presented, on April 3, one of the two Gold Heart Awards for outstanding contributions to the advancement of cardiovascular medicine and the Heart Program to Dr. Sprague, who is Clinical Associate in Medicine at Harvard Medical School and a Past President of the Association. Dr. Sprague's citation declared that "his humanity, vision and practical wisdom have been of great significance in the shaping of organizational policy, and in winning support of medical science and the public for the objectives of the Association."

Dr. King, retiring President, who now becomes Chairman of the Association's Scientific Council, is Chief of Medical Service of the Virginia Mason Hospital in Seattle and Clinical Associate Professor of Medicine at the University of Washington School of Medicine as well as Consultant in Cardiology to the Department of Health, Territory of Alaska.

Dr. Leroy E. Burney, F.A.C.P., Indianapolis, has recently received the Indiana State Junior Chamber of Commerce Good Government Award. Dr. Burney is Secretary and Commissioner of the Indiana State Board of Health. He became affiliated with the U. S. Public Health Service in 1932, and five years later established the first mobile venereal disease clinic service in Brunswick, Ga. Dr. Burney accepted his present post in 1945 and is also Associate Professor of Public Health at the Indiana University School of Medicine. The Junior Chamber of Commerce Award is presented annually "to the governmental official deemed to have conducted the responsibilities of his office in a manner most compatible with the best administrative practices."

Dr. Elmer C. Bartels, F.A.C.P., Boston, presented "High Dosage of Propylthiouracil in the Treatment of Hyperthyroidism" at the annual meeting of the American Goiter Association, held in Boston, April 29–May 1. Drs. Harold G. Wolff, F.A.C.P., and William J. Grace (Associate), New York City, were among those who discussed "Studies on Changes in Nitrogen Excretion During Stressful Life Experiences and Their Relation to Thyroid Function." Lt. Benedict J. Duffy, Jr., (MC), USNR, (Associate), Washington, D. C., was the co-author of "Invasive Papillary Cancer of the Thyroid."

Dr. Ramón Suárez, F.A.C.P., San Juan, P. R., Third Vice President of the American College of Physicians, was the official representative of the College at the Second Congress of Cardiology of the SIBIC (La Sociedad de Internos y Becarios del Instituto Nacional de Cardiología de México), held in Acapulco, Mexico, April 21–24. Dr. Ignacio Chávez, F.A.C.P., Mexico City, College Governor for Mexico, is Honorary President of the Society and of the Congress. Participants included Drs. Paul D. White, F.A.C.P., Boston, Mass., George R. Herrmann, III, F.A.C.P., Galveston, Tex., Demetrio Sodi-Pallares, F.A.C.P., Mexico, D. F., Mario Salazar Mallén, F.A.C.P., Mexico, D. F., George C. Griffith, F.A.C.P., Pasadena, Calif., and Robert W. Wilkins, F.A.C.P., Boston.

Dr. Kenneth D. A. Allen, F.A.C.P., Denver, was recently named to a four-year term on the Board of Chancellors of the American College of Radiology. Dr. Allen is Clinical Professor of Radiology at the University of Colorado School of Medicine.

Dr. Robert L. Grissom, F.A.C.P., Omaha, has recently been appointed a full-time Associate Professor in the Department of Internal Medicine at the University of Nebraska College of Medicine.

Dr. Joseph W. Rastetter, F.A.C.P., Milwaukee, Wis., has been appointed Associate Professor of Medicine and Assistant Director of the Department of Medicine at Marquette University School of Medicine.

Dr. Charles L. Brown, F.A.C.P., Philadelphia, was the guest speaker at a monthly meeting of the Kanawha Medical Society, held in Charleston, W. Va., March 9. His topic was "Vagaries of Hypertension and Their Influence on the Selection of Medical and Surgical Treatment."

Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., who takes office this month as President of the American Medical Association, was one of the principal guest speakers at the 104th Annual Session of the Medical Association of Georgia, held in Macon, May 2–5, under the Presidency of Dr. William P. Harbin, Jr., F.A.C.P., of Rome. Dr. Martin's subjects were "Legislative Activities of the AMA" and "Your AMA Is What You Make It." Other guest speakers and their topics included Dr. Arthur R. Colwell, Sr., F.A.C.P., Chicago, Chairman of the Department of Medicine, Northwestern University Medical School, "Selective Treatment of Diabetes Mellitus According to Severity"; and Dr. Edgar Hull, F.A.C.P., New Orleans, Head of the Department of Medicine, Louisiana State University School of Medicine, "Outlook in Patients with Myocardial Infarction."

Dr. Ovid O. Meyer, F.A.C.P., Madison, Professor of Medicine at the University of Wisconsin Medical School, spoke on "The Treatment of Thromboembolic Disease" at a joint meeting of the North Side branch of the Chicago Medical Society and Chicago Heart Association on April 1. Dr. Wright R. Adams, F.A.C.P., Professor of Medicine at the University of Chicago School of Medicine, was one of the discussants.

Dr. Norman H. Jolliffe, F.A.C.P., New York City, gave a presentation on "Recent Developments in Human Nutrition" at the Second Conference on Human Nutrition. The Conference, held March 31–April 1 on the campus of Ohio State University, Columbus, was jointly sponsored by the Ohio Nutrition Committee, the Ohio Department of Health, the Institute of Nutrition and Food Technology of Ohio State University, and the Society of Sigma Xi.

Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., was among the invited speakers at a meeting of the Central Region of the American College of Gastroenterology in Milwaukee on March 28. His presentation was entitled "Management of Benign Ulcerative Intestinal Disease." Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., President of the American College of Gastroenterology, presided at the opening scientific session.

Dr. Vincent J. Derbes, F.A.C.P., New Orleans, La., has been elected a member of the Sub-specialty Board in Allergy of the American Board of Internal Medicine, for a term of five years.

Dr. Russell L. Cecil, F.A.C.P., New York City, was appointed April 3 as Medical Director of the Arthritis and Rheumatism Foundation. Emeritus Professor of Clinical Medicine at Cornell University Medical College, Dr. Cecil will continue to devote half his time to private practice.

Lt. Col. Jack C. Shrader, (MC), USAF, (Associate), has recently been awarded the Bronze Star medal for his outstanding service in Korea, where he was Commander of a medical group and was in charge of an Air Force Hospital. The presentation was made by the Commandant of the Air Force School of Aviation Medicine at Randolph Air Force Base, Tex., where Col. Shrader is Head of the Department of Internal Medicine.

Dr. Edward D. Levy (Associate), Norfolk, has recently been elected Vice President of the Virginia Society of Pathology and Laboratory Medicine.

At the Eighth Annual Meeting held recently in Washington, D. C., Dr. Worth B. Daniels, Sr., F.A.C.P., Washington, was chosen Vice President of the Society of Medical Consultants to the Armed Forces.

The American College of Chest Physicians formed a Hawaiian Chapter in Honolulu last December. Dr. Hastings H. Walker, F.A.C.P., and Dr. Frederick L. Giles, F.A.C.P., both of Honolulu, are President and Secretary-Treasurer, respectively.

Dr. Chesley Bush, F.A.C.P., Inverness, Calif., a former President of the National Tuberculosis Association, has recently been appointed Acting Chief of the Bureau of Tuberculosis Control of the California Department of Public Health while Dr. Edward Kupka, F.A.C.P., Berkeley, is on a two-year leave of absence. Under the foreign aid program, Dr. Kupka is serving as public health adviser to the Vietnam Government during 1954–55. His current address is c/o The American Consulate, Hanoi, Vietnam, French Indochina.

Dr. Maurice B. Strauss, F.A.C.P., Boston, spoke on "Metabolism and Fluid Balance as It Affects the Thoracic Surgeon, the Cardiologist, and the Internist" at the spring meeting of the Connecticut Trudeau Society, held May 26 in Newington.

Dr. A. Dudley Dennison, Jr., F.A.C.P., Indianapolis, Ind., addressed the Richmond Academy of Medicine on March 9, his subject being "Diagnosis of Unusual Complications Following Myocardial Infarction."

Drs. Charles M. Caravati, F.A.C.P., College Governor for Virginia, Harry Walker, F.A.C.P., and W. Taliaferro Thompson, Jr., F.A.C.P., all of Richmond, were guest speakers at the Medical Section of the Second Annual Scientific Assembly of the West Virginia Academy of General Practice, held in Charleston, May 1–2. Their respective topics were "Present Concept of the Management of Hepatitis and Cirrhosis," "Friedlander's Pneumonia," and "Office Management of the Neurasthenic Patient."

Dr. Howard B. Sprague, F.A.C.P., Boston, discussing "The Management of Disorders of the Heart Beat," was one of the principal speakers at the Sixth Annual Meeting of the Pennsylvania Academy of General Practice, held in Wernersville, May 14–16. Other guests and their topics included Dr. Francis D. Murphy, F.A.C.P., Milwaukee, Wis., "Acute Renal Failure"; and Dr. Gene H. Stollerman (Associate), Irvington-on-Hudson, N. Y., "Prevention of Rheumatic Fever."

Dr. Lowell T. Coggeshall, F.A.C.P., Chicago, Dean of the University of Chicago School of Medicine, presided at the 39th Annual Meeting of the Industrial Medical Association, held in Chicago in April. The meeting was centered around a panel discussion on "The Modern Corporation and the Nation's Health" and was sponsored by the Medical Advisory Committee to Industry of the National Fund for Medical Education. Dr. Robert Collier Page, F.A.C.P., New York City, President-Elect of the Industrial Medical Association, was also among the principal speakers and discussed the mounting rôle of industrial medicine in promoting the health of American workers.

Dr. Louis F. Bishop, F.A.C.P., New York City, spoke on "Complications of Myocardial Infarction" at a recent meeting of the New London (Conn.) Heart Association in New London.

Dr. Herbert R. Edwards, F.A.C.P., New York City, addressed the annual meeting of the Puerto Rican Tuberculosis Association, held in San Juan, April 2–3. Dr. Edwards, who is Executive Director of the New York Tuberculosis and Health Association, had been invited by the President of the Puerto Rican Tuberculosis Association to discuss the Puerto Rican problem in New York City.

Under the Presidency of Dr. Robert N. Larimer, F.A.C.P., Sioux City, the Iowa State Medical Society held its annual meeting in Des Moines, April 25–28. Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., incoming President of the American Medical Association, was one of the principal speakers. Other guests included Drs. Joseph B. Kirsner, F.A.C.P., Chicago, and Howard M. Odel, F.A.C.P., Rochester, Minn., whose respective topics were "Current Trends in the Treatment of Peptic Ulcer" and "Basic Considerations in the Treatment of Renal Disease."

Under the joint auspices of the Florida State Board of Health, the Heart Association of Greater Miami, and the Florida Heart Association, the Third Biennial Cardiovascular Seminar was held in Miami Beach, April 29–May 1, immediately following the annual meeting of the Florida Medical Association, April 26–28. Among the speakers were Drs. Charles A. Poindexter, F.A.C.P., New York City, E. Cowles Andrus, F.A.C.P., Baltimore, and Gene H. Stollerman (Associate), Irvington-on-Hudson, N. Y.

At the meeting of the State Association, under the Presidency of Dr. Frederick K. Herpel, F.A.C.P., Palm Beach, Dr. Wilburt C. Davison, F.A.C.P., Durham, N. C., delivered an address entitled "Changes in Medical Education and Patient Care."

Dr. Alvis E. Greer, F.A.C.P., Houston, Tex., President of the American College of Chest Physicians, presented "A Discussion of Certain Preliminary Aspects of Pulmonary Mycotic Disease" before the members of the Florida Chapter of the American College of Chest Physicians, which met April 25, immediately preceding the annual session of the Association.

Dr. John H. Skavlem, F.A.C.P., Cincinnati, was one of the participants in a discussion of "Follow-Up on Positive Survey Films, TB, Cancer, Etc.," which was part of the program of the combined meeting of the Illinois Tuberculosis Association and Illinois Trudeau Society when they met April 29–30 in Peoria.

"Surgery of Acquired Heart Disease" was the symposium sponsored April 13 by the New York Society for Circulatory Diseases. Dr. O. Henry Janton, Jr. (Associate), Philadelphia, spoke on "Pertinent Prognostic Factors in the Selection of Patients with Acquired Heart Disease for Surgery." The meeting was held at the New York Academy of Medicine, with Dr. Simon Dack, F.A.C.P., New York City, presiding.

Drs. John M. Sheldon, F.A.C.P., Ann Arbor, Mich., John L. Sims, F.A.C.P., Madison, Wis., and Harold G. Trimble, F.A.C.P., Oakland, Calif., were among the guest speakers at the annual session of the Arizona Medical Association, which was held April 25–28 in Chandler.

In collaboration with several other state organizations, the State Medical Society of Wisconsin presented a series of postgraduate courses, April 27–29, in Platteville, Oconomowoc, and Manitowoc. Among the instructors was Dr. Howard F. Root, F.A.C.P., Boston, who discussed "Diabetic Emergencies."

Dr. John E. Deitrick, F.A.C.P., Philadelphia, was one of the participants in a symposium, "How Can We Reduce the Cost of Medical Education?", which was part of the annual meeting program of the American Surgical Association when it convened in Cleveland, April 28–30.

"Treatment of Meningitis" was the subject used by Dr. Adolph L. Sahs, F.A.C.P., Iowa City, in addressing the Sixth Annual Meeting of the American Academy of Neurology, which met in Washington, D. C., April 26–May 1.

At the 156th Annual Meeting of the Medical and Chirurgical Faculty of the State of Maryland, Dr. Richard A. Kern, F.A.C.P., Philadelphia, Secretary-General of the College, delivered the I. Ridgeway Trimble Fund Lecture, "Our Growing Responsibilities to the Aged in Our Midst." Drs. Joseph T. Beardwood, Jr., F.A.C.P., and Garfield G. Duncan, F.A.C.P., both of Philadelphia, participated in a diabetes panel, which was moderated by Dr. J. Sheldon Eastland, F.A.C.P., Baltimore. Dr. Paul Dudley White, F.A.C.P., Boston, gave the John M. T. Finney Fund Lecture, "Clues in Cardiovascular Diagnosis and Treatment," and Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, discussed "Certain Advances in Cancer Research." The meeting was held in Baltimore, April 26–28.

Dr. J. Burns Amberson, F.A.C.P., New York City, Professor of Medicine at Columbia University College of Physicians and Surgeons, gave the annual Joseph H. Pratt Lecture of the New England Center Hospital, Boston, on April 28. His subject was "Some Experiences in the Treatment of Tuberculosis."

The annual meeting of the Arkansas Medical Society was held at Fort Smith, April 19–21. Out-of-state speakers and their topics included Dr. Elmer G. Wakefield, F.A.C.P., Rochester, Minn., "Differential Diagnosis Between Organic and Functional Disease of the Intestine"; Dr. James F. Lewis, F.A.C.P., Columbus, Miss., "Anticoagulant Therapy: A Review"; and Dr. William R. Mathews, F.A.C.P., Shreveport, La., "The Changing Face of Medicine in a Morgue During the Last Quarter of a Century."

Dr. Howard A. Rusk, F.A.C.P., New York City, spoke on "Dynamic Recreation —An Essential in Rehabilitation" at the national meeting of the American Association for Health, Physical Education, and Recreation, held in New York City, April 19–23.

Dr. Harry F. Dowling, F.A.C.P., Chicago, Professor of Medicine at the University of Illinois College of Medicine, discussed "Recent Advances in Antibiotic Therapy" on April 23 in Charlotte, N. C. His lecture was presented by the Nalle Clinic Foundation under the sponsorship of the Lucius G. Gage Fund.

Dr. Hans Lisser, F.A.C.P., San Francisco, Clinical Professor of Medicine at the University of California School of Medicine, and Dr. Earle M. Chapman, F.A.C.P., Boston, Clinical Associate in Medicine at the Harvard Medical School, were among those who gave Sommer Memorial Lectures at the University of Oregon Medical School, Portland, April 21–23. The Lectures were presented in conjunction with the annual meeting of the University of Oregon Medical School Alumni Association and the Spring Postgraduate Session of the Oregon Academy of General Practice.

At the annual meeting of the American College of Allergists, held in Miami Beach, Fla., April 5–10, Dr. Mayer A. Green, F.A.C.P., Pittsburgh, Pa., presented a paper entitled "One Year's Experience with Sustained Release Antihistamine Medication—An Experimental and Clinical Study." Retiring First Vice President of the Association, Dr. Green also participated in a round-table discussion of asthma and served as Chairman of a General Session in the meeting and the Postgraduate Instructional Course.

Dr. J. Warrick Thomas, F.A.C.P., Richmond, Va., served as moderator for a round-table luncheon discussion, "Pitfalls in the Diagnosis and Management of Asthma," and Dr. Hyman Miller (Associate), Beverly Hills, Calif., moderated a panel on psychosomatic allergy and also presided at a discussion of "Psychotherapeutic Group Interview with the Parents of Allergic Children."

In the psychosomatic workshops on emotional factors in allergic disorders were included the following: "Psychoanalytically Oriented Interviews—Tape Recording," Dr. M. Murray Peshkin, F.A.C.P., New York City; "Actual Diagnostic Play Session with an Allergic Child," Dr. Hal M. Davison, F.A.C.P., Atlanta; and "Tape Recordings of Interviews with Allergic Patients," Dr. Homer E. Prince, F.A.C.P., Houston, Tex.

The International Association of Medical Museums presented a course in pathological physiology and surgical pathology of the liver as part of its annual meeting in Philadelphia, April 6–7. Participating physicians included Drs. Paul György, F.A.C.P., Philadelphia; Irving B. Brick (Associate), I. Nathan Dubin, F.A.C.P., and James E. Ash, F.A.C.P., Washington, D.C.; Leon Schiff, F.A.C.P., Cincinnati; Charles S. Davidson, F.A.C.P., Boston; Hans Popper, F.A.C.P., Chicago; and Gerald Klatskin, F.A.C.P., New Haven, Conn.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, speaking on "Endocrine Problems of Childhood," was among the out-of-state speakers at the 96th Annual Session of the Missouri State Medical Association, held in St. Louis, April 4–7. Participating members of the College from St. Louis included Dr. Ralph A. Kinsella, F.A.C.P., who served as moderator of a panel on intervertebral discs, and Dr. Daniel L. Sexton, F.A.C.P., and Dr. Paul O. Hagemann, who presided at round-table luncheon discussions.

Dr. Johannes M. Nielsen, F.A.C.P., Los Angeles, was one of the principal speakers at a joint meeting of the Illinois Psychiatric Society and the Chicago Neurological Society, held April 13 in Chicago. His topic was "Neurological Aspects of Psychic Functions."

Dr. Walsh McDermott, F.A.C.P., New York City, addressed the Boston University Chapter of Alpha Omega Alpha on April 14, his subject being "Experimental Basis of the Chemotherapy of Tuberculosis."

Dr. Leonard A. Scheele, F.A.C.P., Washington, D. C., Surgeon General of the U. S. Public Health Service, was the banquet speaker at the annual Cancer Day of the Genesee County Medical Society, celebrated April 12 at Hurley Hospital, Flint, Mich. Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, and Dr. Osborne A. Brines, F.A.C.P., Detroit, were among those participating in panel discussions and making individual presentations.

Drs. Louis H. Clerf, F.A.C.P., Philadelphia, and Cornelius P. Rhoads, F.A.C.P., New York City, were among the guest speakers at the annual Mid-West Cancer Conference, sponsored by the Kansas Division of the American Cancer Society and the Committee on Control of Cancer of the Kansas Medical Society, and held in Wichita, April 1–2.

Drs. Harry F. Dowling, F.A.C.P., and Arthur R. Colwell, Sr., F.A.C.P., both of Chicago, were two of the out-of-state speakers at the Second Annual Postgraduate Assembly, held at the University of Nebraska College of Medicine, Omaha, March 29–31. Their respective subjects were "Rational Antibiotic Therapy" and "Selective Treatment of Diabetes Mellitus According to Severity."

Drs. Morris B. Bender, F.A.C.P., New York City, Henry L. Bockus, F.A.C.P., Philadelphia, and Henry A. Schroeder, F.A.C.P., St. Louis, are among the distinguished guests who will address the 22nd Annual Assembly of the Omaha Mid-West Clinical Society, to be held Oct. 25–28, 1954.

Under the Chairmanship of Dr. K. K. Chen, F.A.C.P., Indianapolis, Ind., the Federation of American Societies for Experimental Biology met in Atlantic City, N. J., April 12–16. Included among the speakers was Dr. Rulon W. Rawson, F.A.C.P., New York City, who discussed "Present Concepts of Thyroid Physiology as Revealed with Modern Tools of Study."

Dr. Irving S. Wright, F.A.C.P., New York City, College Governor for Eastern New York, and Dr. Nelson W. Barker, F.A.C.P., Rochester, Minn., will make presentations at the International Conference on Thrombosis and Embolism, to be held in Basle, Switzerland, July 20–24.

Drs. Elmer L. Sevringhaus, F.A.C.P., Nutley, N. J., Frank H. Krusen, F.A.C.P., Rochester, Minn., and William Likoff, F.A.C.P., Philadelphia, were some of the guest speakers at the annual meeting of the Ohio State Medical Association, held in Columbus, April 12–15. Dr. Sevringhaus' subject was "Prescribing Adequate Nutrition"; Dr. Krusen spoke on "Physical Medicine and Rehabilitation for Chronic Illness"; and Dr. Likoff discussed "Newer Concepts of Coronary Circulation."

Dr. George F. Schmitt, F.A.C.P., Miami, Fla., has been appointed Assistant Clinical Professor of Pharmacology at the new School of Medicine of the University of Miami.

Dr. Schmitt has also been appointed Chairman of the Scientific Exhibits Committee for the Clinical Session of the American Medical Association, to be held in Miami in late November.

Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill., College Regent, has recently been named the recipient of the distinguished Richard T. Crane Professorship in Medicine at the University of Chicago.

Dr. George A. Hellmuth, F.A.C.P., Chicago, Ill., has recently been appointed Associate Clinical Professor of Medicine and Chief of the Cardiovascular Section in the Department of Medicine, Marquette University School of Medicine, Milwaukee, Wis. Dr. Hellmuth, who is currently Assistant Clinical Professor of Medicine at the Stritch School of Medicine of Loyola University, will assume his new duties Sept. 1.

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, was elected a member of the Board of Directors of the American Heart Association at their annual meeting in Chicago on April 4. For the past two years Dr. Leaman has served on the Executive Committee of the Section on Clinical Cardiology of the A.H.A. and will represent this group on the Board.

Rear Adm. Frederick R. Lang, (MC), USN, Retired, F.A.C.P., has recently been appointed Medical Director of the Pennsylvania State Sanatorium for Tuberculosis No. 3 at Hamburg. Before his retirement, Adm. Lang was Chief of Medical Service at the U. S. Naval Hospital at Annapolis, Md.

The Honorable John S. Fine, Governor of the Commonwealth of Pennsylvania, has recently appointed Dr. Carl C. Fischer, F.A.C.P., Philadelphia, Chairman of the Governor's Committee on Children and Youth.

Vacancies for Residents

The Veterans Administration Hospital at Houston, Texas, has announced vacancies for two first-year and two second-year residents. This is an 1100-bed Dean's Committee Veterans Administration Hospital of the general medical and surgical type. The Medical Service has 430 beds, including 185 beds in tuberculosis. It is associated intimately with the Baylor University College of Medicine. Presently there are 23 rotating interns and 11 residents in Internal Medicine. The salary is $2,640.00 for first-year residents, $2,970.00 for second-year, and $3,300.00 for third-year. Inquiries should be sent to Dr. H. D. Bennett, F.A.C.P., Chief, Medical Service, Veterans Administration Hospital, 2002 Holcombe Blvd., Houston 31, Tex.

OBITUARIES

DR. LUTHER BACH

Luther Bach, M.D., F.A.C.P., died suddenly on Nov. 28, 1953. He had retired from active practice on July 1, 1952, because of poor health. Dr. Bach was born near Jackson, Ky., on Oct. 19, 1891. He attended Berea College and Eastern Kentucky State Normal School and received the degree of Doctor of Medicine in 1915 from the University of Louisville School of Medicine. His internship was served at the Good Samaritan Hospital, Lexington, Ky. During World War I Dr. Bach served as a First Lieutenant in the Medical Corps of the U. S. Army and was stationed at the base hospital at Camp Sherman, Ohio, in 1917 and later served in France in 1918. He was a member of the medical staff of the Bach Hospital, Jackson, Ky., from 1919 to 1926, and in 1927 he was engaged in public health work in Panama.

In 1928 Dr. Bach established his practice in northern Kentucky, where he remained until his retirement in 1952. During this time he served on the active staffs of Wm. Booth Memorial Hospital and St. Elizabeth Hospital, Covington, and Speers Memorial Hospital, Dayton. He was President of the Campbell-Kenton County Medical Society in 1937, and of the Licking Valley Medical Society in 1938. He served as Councilor of the Kentucky State Medical Association from 1939 to 1940. He was a member of the American Medical Association, the Southern Medical Association and the American Heart Association. He was elected a Fellow of the American College of Physicians in 1941.

Dr. Bach was highly regarded and respected by the members of the medical profession in northern Kentucky. In his passing the community has suffered a distinct loss, and he will be sorely missed by his many friends and patients.

MURRAY L. RICH, M.D., F.A.C.P.

DR. SAMUEL GITLOW

Dr. Samuel Gitlow, a Fellow of the American College of Physicians, died Jan. 6, 1954, of a coronary occlusion in Miami Beach, Fla.

Dr. Gitlow was born Jan. 25, 1889, in New York City, where he spent his active medical life. He received his M.D. degree from the Columbia University College of Physicians and Surgeons in 1912. He carried on research in biochemistry and toxicology from 1912 to 1914 and became a Research Assistant (1917–19) at Columbia University College of Physicians and Surgeons. He was Director of Laboratories of the Bronx Hospital, Associate Pathologist from 1916 to 1941 and Adjunct Physician from 1918 until 1933 at the Lebanon Hospital. At the Lebanon Hospital Dr. Gitlow also served as Chief of the Diabetic Clinic and Biochemistry Department (1931–39), Associate Physician (1933–43), Director of Clinics in 1939, Attending Physician, Director of Diabetic Clinics, and Chief of Metabolic Diseases from 1943 until 1951, at which time he became Consulting Physician on retirement from active practice. He was formerly Attending and later Consulting Physician to the Home and Hospital of the Daughters of Jacob. He was at one time Captain in the Medical Reserve Corps.

Dr. Gitlow was President of the Bronx County Medical Association in 1928, Bronx Pathological Society in 1930, and of the North Bronx Medical Society in 1944. He was Chairman of the Medical Advisory Committee of the North Haven Health Center in 1944. He was a Fellow of the New York Academy of Medicine, a member of the Medical Society of the State of New York, American Medical Association, American Diabetes Association, and the American Association for the Advancement of Science. He was a former member of the Board of Directors of the Neighborhood Health Development, Inc. He became an Associate of the American College

of Physicians in 1925 through membership in the American Congress on Internal Medicine, and in 1944 he was elected a Fellow.

It is with deep regret that we take cognizance of the loss of Dr. Gitlow at this time.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JAMES S. McLESTER

"So when a great man dies
For years beyond our ken
The light he leaves behind him lies
Upon the paths of men."—Longfellow

Dr. James Somerville McLester, F.A.C.P., was born in Tuscaloosa, Ala., Jan. 25, 1877, and died from coronary occlusion in Birmingham, Ala., Feb. 8, 1954.

He received a B.A. degree from the University of Alabama in 1896 and an M.D. degree from the University of Virginia Department of Medicine in 1899. He did postgraduate studies at the Universities of Gottingen and Freiburg, Germany, before becoming Professor of Pathology at the Birmingham Medical College in 1902. He later entered practice in internal medicine in Birmingham and became the Professor of Medicine at the Birmingham Medical College. He studied under Dr. Fredrich Mueller while doing postgraduate work in biochemistry in Berlin and Munich in 1907–08. After the closing of the Birmingham Medical College, Dr. McLester became associated with the University of Alabama in Tuscaloosa in the School of Basic Sciences. He was appointed Professor of Medicine in 1919 and played an active rôle in the School until he became Professor Emeritus of Medicine in 1950.

During the years when there was no medical school in Birmingham, Dr. McLester diligently applied himself to the teaching of interns, residents, and young physicians of his community in the charity wards of the Jefferson-Hillman Hospital. Many of us feel that the inspiration and counsel which he freely gave to the younger physicians of his community to be his greatest contribution to medicine. He took an active part in the organization of the four-year medical school of the University of Alabama, which was opened in Birmingham in 1945.

In World War I he served in the U. S. Armed Forces in France. He was Commanding Officer of Evacuation Hospital No. 18, holding the rank of Major, and later was promoted to Lieutenant Colonel. He was subsequently commissioned Colonel in the Medical Reserve Corps. On his return from military service in 1919, he resumed his practice of medicine in Birmingham and his teaching at the University of Alabama.

Dr. McLester was a widely known authority in metabolism and nutrition and wrote many articles on these subjects. He did extensive research work in foods and feeding, and to him goes much of the credit for making America nutrition conscious. In World War II he was Chairman of the Subcommittee on Nutrition of the National Research Council, which was concerned with the feeding of the Armed Forces. He was also a member of the Food and Nutrition Board of the Council. He served as Chairman of the Health Advisory Council of the Chamber of Commerce of the United States and as a member of the General Advisory Committee of the National Foundation for Infantile Paralysis.

In 1933 he was appointed a member of the Committee on Foods, which was later renamed the Council on Foods and Nutrition, of the American Medical Association. He served continuously on this Council with the exception of the two years that he was President of the American Medical Association. He served as the Council Chairman from 1940 to 1952.

It was in the last few months of his life that he received a signal honor for his lifelong work on nutrition. The Board of Trustees of the American Medical Asso-

ciation, through its Council on Foods and Nutrition, on Nov. 28, 1953, awarded him the Joseph Goldberger award for outstanding contributions in the field of clinical nutrition. Dr. McLester was thus cited for his important rôle in translating the results of nutritional research into human values and integrating nutrition into the teaching of all phases of medicine. He was recently named "Dean of American Nutritionists" by *Today's Health*.

Dr. McLester was active in the American Medical Association, serving as its 88th President. He was Secretary of the Section on the Practice of Medicine of the Association, 1917–18, serving as Chairman of this Section at the annual session in 1920. He served as a member of the House of Delegates of the American Medical Association in 1921 and again from 1929 to 1933. In 1929 he received an honorary doctor of laws degree from the University of Alabama, and in the same year he became a member of the Council on Medical Education and Hospitals, serving until his election to the Presidency of the American Medical Association in 1934.

He became a Fellow of the American College of Physicians in 1928, during a period of reorganization of the College. He served on its Board of Regents for several years and made valuable contributions to the work of the Committee on Credentials for the establishment of high standards of membership.

He was certified by the American Board of Internal Medicine and was a member of many clinical societies: the Association of American Physicians, American Society for Clinical Investigation, and the American Clinical and Climatological Association. He was one of the early active members of the Southern Medical Association and was for some years its Chairman of the Section of Medicine.

He held an honored position in the medical societies of both the county and state. In 1910 he was elected President of the Jefferson County Medical Society and in 1920 he was made President of the Medical Association of the State of Alabama. From 1928 to 1935 he was a member of the State Board of Censors of the Alabama Medical Association and was a member of the State Board of Health. He served as Medical Director of the Birmingham Public Schools and as Physician-in-chief of the Jefferson-Hillman Hospital for many years.

Dr. McLester was author of more than 100 articles on nutrition and metabolism and authored *Nutrition and Diet in Health and Disease*, now in its sixth edition, *The Diagnosis and Treatment of Disorders of Metabolism*, and chapters in various medical books.

Many honors came to Dr. McLester during his lifetime, but of all these he derived the greatest satisfaction from the esteem in which he was held by his former students and residents. In 1950 they presented his portrait to the Medical College of Alabama as a mark of their appreciation of his teaching and leadership. At present it hangs in the library of this school. In his contact with the "young men of medicine," he repeatedly propounded the dicta of medicine that he felt characterized a *good physician* —those of humility, compassion, equanimity and taciturnity. His life and works are a reflection of these principles.

His death on Feb. 8, 1954, comes not only as a great personal loss to his many friends and associates, but it brings to a close a life devoted to his profession and, through it, to his fellow men.

HOWARD L. HOLLEY, M.D., F.A.C.P.

DR. RICHARD J. F. MURPHY

Dr. Richard Joseph Francis Murphy, Associate of the College, died on Feb. 28, 1954, in Montreal, Que.

He was born in Halifax, N. S., on March 27, 1919, was graduated in medicine from Dalhousie University Faculty of Medicine in 1943, and served in the Royal Canadian Navy for three years, retiring with the rank of Surgeon-Lieutenant Com-

mander. Following the war, Dr. Murphy spent five years doing postgraduate work in medicine and cardiology at the Royal Victoria Hospital, Montreal, and at Duke University Hospital, Durham, N. C. He was appointed Assistant in the Outdoor Clinic at the Royal Victoria Hospital in 1951 and was promoted to Clinical Assistant in 1953. He was a Lecturer in Medicine on the staff of McGill University Faculty of Medicine and a Research Associate in the McGill University Clinic of the Royal Victoria Hospital.

Dr. Murphy won by examination in 1952 the Fellowship of the Royal College of Physicians of Canada. In 1953, the year he became an Associate of the American College of Physicians, Dr. Murphy was granted a medical research fellowship by the Canadian Life Insurance Officers Association and was actively engaged in research in cardiovascular problems at the time of his death.

He was a member of the Montreal Medico-Chirurgical Society and the Montreal Cardiac Society.

Dr. Murphy is survived by his widow, Mrs. Antoinette Murphy, and three children, Brian, Christine and Gavin.

WALTER DEM. SCRIVER, M.D., F.A.C.P.,
Governor for Quebec

DR. SUTHERLAND E. SIMPS

Sutherland Eric Simpson, M.D., F.A.C.P., who had
in May, 1952, because of a cerebral thrombosis, died Janu
N. Y.

Dr. Simpson was born in Edinburgh, Scotland, on
medical training was taken at Cornell University, where
in 1921. Four years later he obtained his M.D. from Har
lowing an internship and residency at the Mattapan Tub
Bent Brigham Hospital in Boston and the Trudeau Sanat
Assistant Resident at the Wisconsin State Sanatorium
1928 and 1929. He then moved to Rochester, N. Y., w
years at the Iola-Monroe County Tuberculosis Sanato
Superintendent and Medical Director of the Jefferson
torium for Chronic Diseases in Watertown, and he held
ment in 1952. Since 1935, he had also been a member
ciate Staffs of the House of the Good Samaritan and Me

In 1940 Dr. Simpson served as President of the San
Board of Managers Association of New York State; an
in his county and state societies, he was a'so a memb
Association, the National Tuberculosis Association, and
ciety. He became a Fellow of the American College of

Dr. Simpson was a very well trained internist. As Director of the Jefferson County Hospital and Sanatorium for Chronic Diseases, he did an excellent job. He had humane interest in patients. The medical profession and the people of Jefferson County have sustained a distinct loss in the death of Dr. Simpson.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

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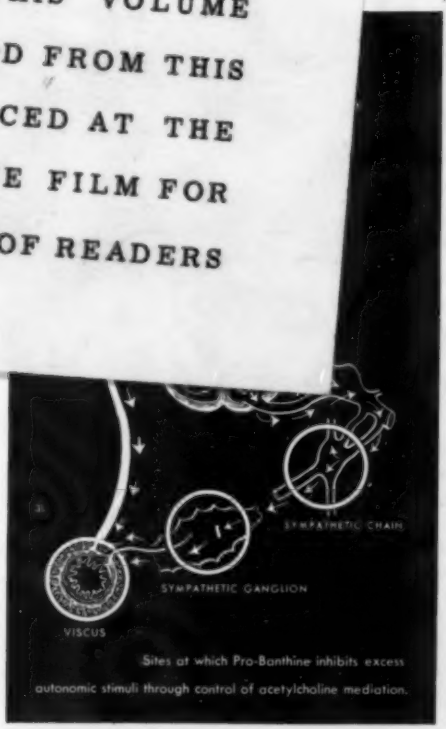
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[illegible] excess motility of the gastroin- [illegible]ide use[1] [illegible]nal diar- [illegible]olitis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.

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Sites at which Pro-Banthine inhibits excess autonomic stimuli through control of acetylcholine mediation.

Roback and Beal[2] administered Pro-Banthine to a series of 156 patients during the period of a year. These authors report that the oral administration of 30 mg. of the drug "resulted in marked and prolonged inhibition of the motility of the stomach, jejunum, and colon. . . ."

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1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: Effect of a New Quaternary Ammonium Compound on Gastric Secretion and Gastrointestinal Motility, Gastroenterology *25*:24 (Sept.) 1953.

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WALTER DEM. SCRIVER, M.D., F.A.C.P.,
Governor for Quebec

DR. SUTHERLAND E. SIMPSON

Sutherland Eric Simpson, M.D., F.A.C.P., who had retired from active practice in May, 1952, because of a cerebral thrombosis, died January 8, 1954, in Watertown, N. Y.

Dr. Simpson was born in Edinburgh, Scotland, on June 11, 1898. His premedical training was taken at Cornell University, where he received his A.B. degree in 1921. Four years later he obtained his M.D. from Harvard Medical School. Following an internship and residency at the Mattapan Tuberculosis Hospital and Peter Bent Brigham Hospital in Boston and the Trudeau Sanatorium, Dr. Simpson became Assistant Resident at the Wisconsin State Sanatorium in Waukesha County during 1928 and 1929. He then moved to Rochester, N. Y., where he spent the next five years at the Iola-Monroe County Tuberculosis Sanatorium. In 1934 he became Superintendent and Medical Director of the Jefferson County Hospital and Sanatorium for Chronic Diseases in Watertown, and he held this position until his retirement in 1952. Since 1935, he had also been a member of the Attending and Associate Staffs of the House of the Good Samaritan and Mercy Hospital.

In 1940 Dr. Simpson served as President of the Sanatorium Superintendents and Board of Managers Association of New York State; and in addition to memberships in his county and state societies, he was also a member of the American Medical Association, the National Tuberculosis Association, and the American Trudeau Society. He became a Fellow of the American College of Physicians in 1941.

Dr. Simpson was a very well trained internist. As Director of the Jefferson County Hospital and Sanatorium for Chronic Diseases, he did an excellent job. He had humane interest in patients. The medical profession and the people of Jefferson County have sustained a distinct loss in the death of Dr. Simpson.

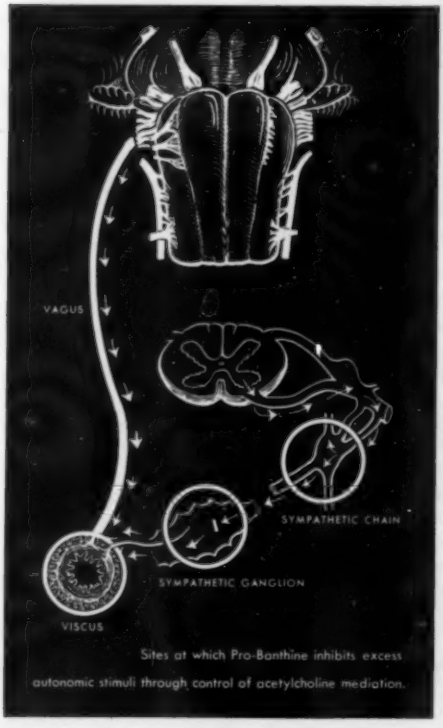
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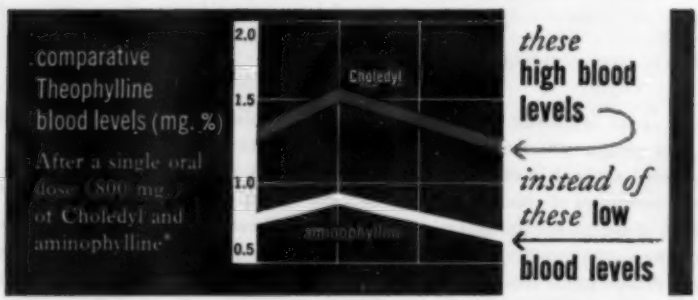
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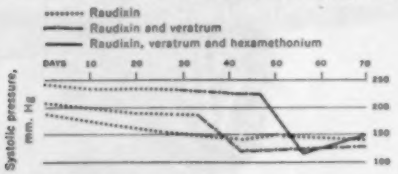
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1. WILKINS, R. W., AND JUDSON, W. E.: NEW ENGLAND J. MED. 248:48, 1953.
2. FREIS, E. D.: M. CLIN. NORTH AMERICA 38:163, 1954.

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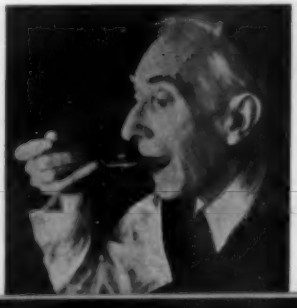
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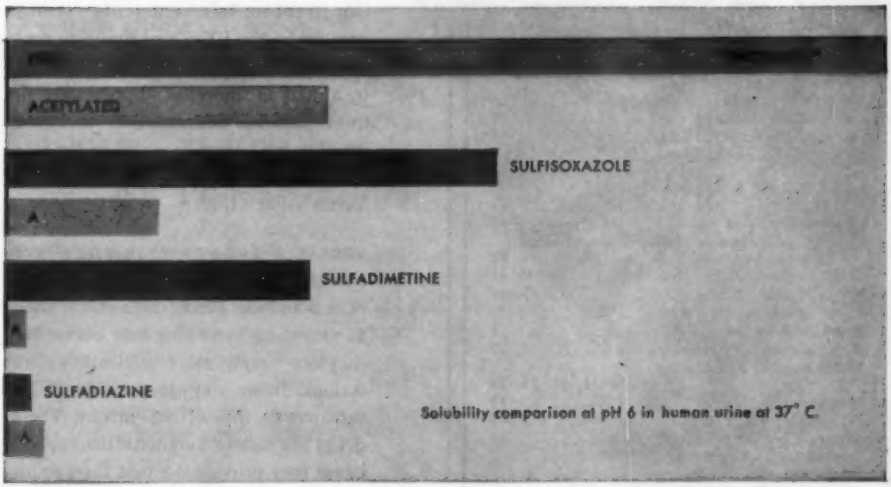
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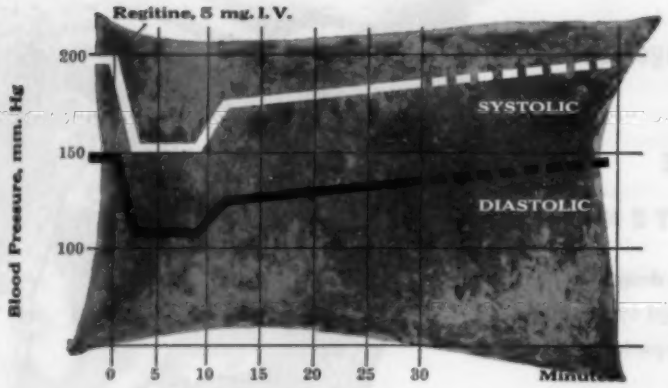
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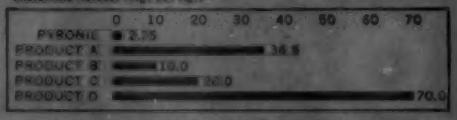
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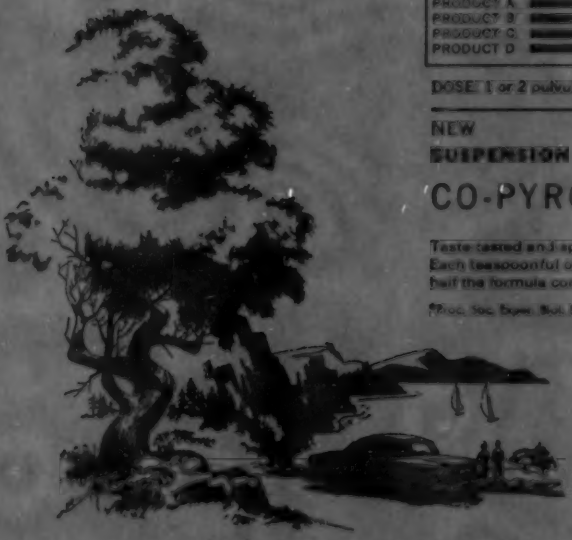
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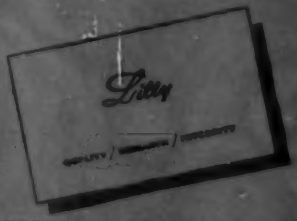
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